7. PASSIVE SMOKING AND RESPIRATORY DISORDERS OTHER THAN CANCER

7.1. INTRODUCTION

In 1984, a report of the Surgeon General identified cigarette smoking as the major cause of chronic obstructive lung disease in the United States (U.S. DHHS, 1984). The same report stated that there is conclusive evidence showing that smokers are at increased risk of developing respiratory symptoms such as chronic cough, chronic phlegm production, and wheezing (U.S. DHHS, 1984). More recently, longitudinal studies have demonstrated accelerated decline in lung function in smoking adults (Camilli et al., 1987). In children and adolescents who have recently taken up smoking, several cross-sectional studies have found statistically significant increases in the prevalence of respiratory symptoms (cough, phlegm production, and dyspnea [i.e., shortness of breath]) (Seely et al., 1971; Bewley et al., 1973). Longitudinal studies also have demonstrated that, among young teenagers, functional impairment attributable to smoking may be found after as little as 1 year of smoking 10 or more cigarettes per week (Woolcock et al., 1984).

From a pathophysiologic point of view, smoking is associated with significant structural changes in both the airways and the pulmonary parenchyma (U.S. DHHS, 1984). These changes include hypertrophy and hyperplasia of the upper airway mucus glands, leading to an increase in mucus production, with an accompanying increased prevalence of cough and phlegm. Chronic inflammation of the smaller airways leads to bronchial obstruction. However, airway narrowing also may be due to the destruction of the alveolar walls and the consequent decrease in lung elasticity and development of centrilobular emphysema (Bellofiore et al., 1989). Smoking also may increase mucosal permeability to allergens. This may result in increased total and specific IgE levels (Zetterstrom et al., 1981) and increased blood eosinophil counts (Halonen et al., 1982).

The ascertained consequences of active smoking on respiratory health, and the fact that significant effects have been observed at relatively low-dose exposures, lead to an examination for similar effects with environmental tobacco smoke (ETS). Unlike active smoking, involuntary exposure to ETS (or "passive smoking") affects individuals of all ages, particularly infants and children. An extensive analysis of respiratory effects of ETS in children suggests that the lung of the young child may be particularly susceptible to environmental insults (NRC, 1986). Exposures in early periods of life during which the lung is undergoing significant growth and remodeling may alter the pattern of lung development and increase the risk for both acute and chronic respiratory illnesses.

Acute respiratory illnesses are one of the leading causes of morbidity and mortality during infancy and childhood. One-third of all infants have at least one lower respiratory tract illness (bronchitis, bronchiolitis, croup, or pneumonia) during the first year of life (Wright et al., 1989),

whereas approximately one-fourth have these same illnesses during the second and third years of life (Gwinn et al., 1991). The high incidence of these potentially severe illnesses has an important consequence from a public health viewpoint: Even small increases in risk due to passive exposure to ETS would considerably increase the absolute number of cases in the first 3 years of life (see Chapter 8). In addition, several studies have shown that lower respiratory tract illnesses occurring early in life are associated with a significantly higher prevalence of asthma and other chronic respiratory diseases and with lower levels of respiratory function later in life (reviewed extensively by Samet and collaborators [1983]).

This chapter reviews and analyzes epidemiologic studies of noncancer respiratory system effects of passive smoking, starting with possible biological mechanisms (Section 7.2). The evidence indicating a relationship between exposure to ETS during childhood and acute respiratory illnesses (Section 7.3), middle ear diseases (Section 7.4), chronic respiratory symptoms (Section 7.5), asthma (Section 7.6), sudden infant death syndrome (Section 7.7), and lung function impairment (Section 7.8) is evaluated. Passive smoking as a risk factor for noncancer respiratory illnesses and lower lung function in adults also is analyzed (Section 7.9). A health hazard assessment and population impact is presented in the next chapter.

7.2. BIOLOGICAL MECHANISMS

7.2.1. Plausibility

It is plausible that passive smoking may produce effects similar to those known to be elicited by active smoking. However, several differences both between active and passive forms of exposure and among the individuals exposed to them need to be considered.

The concentration of smoke components inhaled by subjects exposed to ETS is small compared with that from active smoking. Therefore, effect will be highly dependent on the nature of the dose-response curve (NRC, 1986). It is likely that there is a distribution of susceptibility to the effects of ETS that may depend on, among other factors, age, gender, genetic predisposition, respiratory history, and concomitant exposure to other risk factors for the particular outcome being studied. The ability to ascertain responses to very low concentrations also depends on the reliability and sensitivity of the instruments utilized.

Breathing patterns for the inhalation of mainstream smoke (MS) and ETS differ considerably; active smokers inhale intensely and intermittently and usually hold their breath for some time at the end of inspiration. This increases the amount of smoke components that are deposited and absorbed (U.S. DHHS, 1986). Passive smokers inhale with tidal breaths and continuously. Therefore, patterns of particle deposition and gas diffusion and absorption differ considerably for these two types of inhalation.

influence on that decision of events occurring shortly after birth (such as respiratory illnesses in their child) cannot be excluded. Recall bias also may influence the results of retrospective studies claiming differential effects on lung function of prenatal and postnatal maternal smoking habits (Yarnell and St. Leger, 1979).

To attempt to circumvent these problems, researchers have studied infant lung function shortly after birth (the youngest group of infants reported was 2 weeks old [Neddenriep et al., 1990]), with the implication that subsequent changes encountered could be attributed mainly to ETS exposure. However, the possibility that even brief exposure to ETS may affect the lungs at a highly susceptible age may not be discarded. Maternal smoking during pregnancy needs to be considered, therefore, as a potential modifier of the effect of passive smoking on respiratory health, particularly in children.

Exposure to compounds present in tobacco smoke may affect the fetal and neonatal lung and alter lung structure much like these same compounds do in smoking adults. Neddenriep and coworkers (1990) studied 31 newborns and reported that those whose mothers smoked during pregnancy had significant increases in specific lung compliance (i.e., lung compliance/lung volume) at 2 weeks of age when compared with infants of nonsmoking mothers. The authors concluded that exposure to tobacco products detrimentally affects the elastic properties of the fetal lung. Although these effects also could be attributed to postnatal exposure to ETS, it is unlikely that such a brief period of postnatal exposure would be responsible for these changes affecting the lung parenchyma (U.S. DHHS, 1986).

There is evidence for similar effects of prenatal lung development in animal models. Collins and associates (1985) exposed pregnant rats to MS during day 5 to day 20 of gestation. They found that pups of exposed rats showed reduced lung volume, reduced number of lung saccules, and reduced length of elastin fibers in the lung interstitium. This apparently resulted in a decrease in lung elasticity: For the same inflation pressure, pups of exposed mothers had significantly higher weight-corrected lung volumes than did pups of unexposed mothers. Vidic and coworkers (1989) exposed female rats for 6 months (including mating and gestation) to MS. They found that lungs of their 15-day-old pups had less parenchymal tissue, less extracellular matrix, less collagen, and less elastin than found in lungs of control animals. This may explain the increased lung compliance observed by Collins et al. (1985) in pups exposed to tobacco smoke products in utero.

Hanrahan and coworkers (1990) reported that infants born to smoking mothers had significantly reduced levels of forced expiratory flows. The researchers studied 80 mother/child pairs and found significant correlations between the cotinine/creatinine ratio in urine specimens obtained during pregnancy in the mother and maximal expiratory flows and tidal volumes at a

There are also important differences in the physicochemical properties of ETS and MS (see Chapter 3). These have been extensively reviewed earlier by the National Research Council (NRC, 1986) and the Surgeon General (U.S. DHHS, 1986). ETS is a combination of exhaled MS, sidestream smoke (that is, the aerosol that is emitted from the burning cone between puffs), smoke emitted from the burning side of the cigarette during puffs, and gases that diffuse through the cigarette paper into the environment. This mixture may be modified by reactions that occur in the air before involuntary inhalation. This "aging" process includes volatilization of nicotine, which is present in the particulate phase in MS but is almost exclusively a component of the vapor phase of ETS. Aging of ETS also entails a decrease in the mean diameter of its particles from 0.32 μm to 0.1-0.14 μm, compared to a mean particle diameter for MS of 0.4 μm (NRC, 1986).

Individual and socioeconomic susceptibility may be important determinants of possible effects of ETS on respiratory health. A self-selection process almost certainly occurs among subjects who experiment with cigarettes, whereby those more susceptible to the irritant or sensitizing effects of tobacco smoke either never start or quit smoking (the so-called "healthy smoker" effect). Infants, children, and nonsmoking adults thus may include a disproportionate number of susceptible subjects when compared with smoking adults. In addition, recent studies clearly have shown that, as incidence and prevalence of cigarette smoking has decreased, the socioeconomic characteristics of smokers also have changed. Among smokers, the proportion of subjects of lower educational level has increased in the past 20 years (Pierce et al., 1989). The female-to-male ratio also has increased (Fiore et al., 1989), and this is particularly true for young, poor women, in whom incidence and prevalence of smoking has increased (Williamson et al., 1989). It is thus possible that exposure to ETS may be most prevalent today among precisely those infants and children who are known to be at a high risk of developing respiratory illnesses early in life.

7.2.2. Effects of Exposure In Utero and During the First Months of Life

A factor that may significantly modify the effect of passive smoking (particularly in children) is exposure to tobacco smoke components by the fetus during pregnancy. This type of exposure differs considerably from passive smoking; in fact, the fetus (including its lungs) is exposed to components of tobacco smoke that are absorbed by the mother and that cross the placental barrier, whereas passive smoking directly affects the bronchial mucosa and the alveolus. It is difficult to distinguish between the possible effects of smoking during pregnancy and those of ETS exposure after birth. Some women may quit smoking during pregnancy, only to resume after pregnancy is over. Most mothers who smoke during pregnancy continue smoking after the birth of their child (Wright et al., 1991), and among those who stop smoking after birth, the

postconceptional age of 50 weeks or younger in their children. The investigators concluded that exposure due to prenatal smoking diminishes infant pulmonary function at birth and, by inference, airway size. These authors also measured maximal flows during tidal breathing in their subjects. At rather low lung volumes, such as those present during tidal breathing, airway size and maximal flows are both a function of lung elasticity. These results thus may be due to both a specific alteration of the infant's airways and an increased lung compliance in infants whose lungs are small relative to the infant's length.

It also has been suggested that the increased IgE levels observed in adult smokers also may be present in fetuses whose mothers smoke during pregnancy. Magnusson (1986) reported that cord serum levels of IgE and IgD were significantly higher for neonates whose mothers smoked during pregnancy, particularly if the neonates had no parental history of allergic disorders. Cord serum levels of IgD (but not of IgE) were increased for neonates whose fathers smoked, and this effect was independent of maternal smoking. A more recent study on a larger sample (more than 1,000 neonates) failed to find any significant difference in cord serum IgE levels between infants (N = 193) of mothers who smoked during pregnancy and those (N = 881) of mothers who did not (Halonen et al., 1991).

It also has been reported recently that the pulmonary neuroendocrine system may be altered in infants whose mothers smoke during pregnancy. The pulmonary neuroendocrine system, located in the tracheobronchial tree, consists of specialized cells (isolated or in clusters called "neuroepithelial bodies") that are closely related to nerves. In humans, these cells increase in number significantly during intrauterine development, reach a maximum around birth, and then rapidly decline during the first 2 years of life. Their function is not well understood, but the presence of potent growth factors and bronchoconstrictive substances in their granules suggests that they play an important role in growth regulation and airway tone control during this period of lung development (Stahlman and Gray, 1984). Chen and coworkers (1987) reported that maternal smoking during pregnancy increases the size of infant lung neuroepithelial bodies and decreases the amount of core granules present in them. Wang and coworkers (1984) had reported previously that mother mice receiving tap water with nicotine during pregnancy and during lactation had offspring with increased numbers of neuroepithelial bodies at 5 days of age when compared with baby mice whose mothers were not exposed. Baby mice exposed to nicotine only during pregnancy had neuroepithelial bodies of intermediate size with respect to these two groups, whereas those exposed only during lactation had neuroepithelial bodies of normal size. By age 30 days, only baby mice exposed to nicotine during both pregnancy and lactation had neuroepithelial bodies that were larger than those of control animals.

Activation of the pulmonary neuroendocrine system is not limited to ETS exposure; it is activated by active smoking as well. Aguayo and collaborators (1989) reported that bronchoalveolar lavage fluids obtained from healthy smokers have increased levels of bombesin-like peptides, which are a normal component and a secretion product of human lung neuroendocrine cells (Cutz et al., 1981).

In summary, effects of maternal smoking during pregnancy on the fetus are difficult to distinguish from those elicited by early postnatal exposure to ETS. Animal studies suggest that postnatal exposure to tobacco products enhances the effects of in utero exposure to these same products.

7.2.3. Long-Term Significance of Early Effects on Airway Function

By altering the structural and functional properties of the lung, prenatal exposure to tobacco smoke products and early postnatal exposure to ETS increase the likelihood of more severe complications during viral respiratory infections early in life. Martinez and collaborators (1988a) measured lung function before 6 months of age and before any lower respiratory illness in 124 infants. They found that infants with the lowest levels for various indices of airway size were three to nine times more likely to develop wheezing respiratory illnesses during the first year of life than the rest of the population. The same authors (Martinez et al., 1991) subsequently showed that, in these same infants with lower initial levels of lung function, recurrent wheezing illnesses also were more likely to occur during the first 3 years of life. A similar study performed in Australia (Young et al., 1990) confirmed that infants who present episodes of coughing and wheezing during the first 6 months of life have lower maximal expiratory flows before any such illnesses develop.

The increased likelihood of pulmonary complications during viral respiratory infections in infants of smoking parents has important long-term consequences for the affected individual. There is considerable evidence suggesting that subjects with chronic obstructive lung diseases have a history of childhood respiratory illnesses more often than subjects without such diseases (reviewed by Samet and coworkers [1983]). Burrows and collaborators (1988) found that active smokers without asthma (N = 41) who had a history of respiratory troubles before age 16 years showed significantly steeper declines in FEV_1 (as a percentage of predicted) after the age of 40 than did nonasthmatic smokers without such a history (N = 396). Although these results may have been influenced by recall bias, they suggest that lower respiratory tract illnesses during a period of rapid lung development may damage the lung and increase the susceptibility to potentially harmful environmental stimuli.

There is no information available on the degree of reversibility of changes induced by exposure to ETS during early life. Longitudinal studies of lung function in older children have shown, however, that diminished levels of lung function are found in children of smoking parents at least until the adolescent years.

7.2.4. Exposure to ETS and Bronchial Hyperresponsiveness

Bronchial hyperresponsiveness consists of an enhanced sensitivity of the airways to pharmacologic or physical stimuli that normally produce no changes or only small decreases in lung function in normal individuals. Subjects with bronchial hyperresponsiveness have significant drops in airway conductance and maximal expiratory flows after inhalation of stimuli such as cold air, hypertonic saline, nebulized distilled water, methacholine, or histamine. Bronchial hyperresponsiveness is regarded as characteristic of asthma (O'Connor et al., 1989) and may precede the development of this disease in children (Hopp et al., 1990). It has also been considered as a predisposing factor for chronic airflow limitation in adult life (O'Connor et al., 1989).

Recent studies of large population samples have shown that active smokers have increased prevalence of bronchial hyperresponsiveness (Woolcock et al., 1987; Sparrow et al., 1987; Burney et al., 1987) when compared with nonsmokers. This relationship seems to be independent of other possible determinants of bronchial hyperresponsiveness (O'Connor et al., 1989). However, one large study of almost 2,000 subjects from a general population sample failed to find a significant relationship between smoking and prevalence of bronchial hyperresponsiveness (Rijcken et al., 1987). The subjects involved in the latter study were younger and were therefore exposed to a smaller average cumulative pack-years of smoking than were the subjects of studies in which a positive relationship was found. This suggests that the relationship may be evident only among individuals with a high cumulative exposure.

Epidemiologic studies have demonstrated that exposure to ETS is associated with an increased prevalence of bronchial hyperresponsiveness in children. Murray and Morrison (1986), in a cross-sectional study, reported that asthmatic children of smoking mothers were four times more likely to show increased responsiveness to histamine than were asthmatic children of nonsmoking mothers. O'Connor and coworkers (1987), in a study of a general population sample, found a significant association between maternal smoking and bronchial hyperresponsiveness (as assessed with eucapnic hyperpnea with subfreezing air) among asthmatic children, but not among nonasthmatic children (Weiss et al., 1985). Martinez and coworkers (1988b) reported a fourfold increase in bronchial responsiveness to carbachol among male children of smoking parents when compared with male children of parents who were both nonsmokers. A smaller (and statistically

not significant) increase in bronchial responsiveness was reported in girls. These authors also found that the effect of parental smoking was stronger in asthmatic children, and results were still significant after controlling for this factor in a multivariable analysis. Because only a small proportion of mothers in this population smoked during pregnancy, the effect was considered to be associated mainly with exposure to ETS in these children. Lebowitz and Quackenboss (1990) showed that odds of having bronchial reactivity (as assessed by the diurnal variability in maximal expiratory flow rate) were 3.6 times as high among 18 children aged 15 years and younger who lived with persons who smoked more than 20 cigarettes per day than among 62 children of the same age who lived with nonsmokers (95% C.I. = 1.2, 10.6). Children living with smokers of 1 to 20 cigarettes per day had a prevalence of bronchial reactivity that was similar to that of children living with nonsmokers.

Therefore, there is evidence indicating that parental smoking enhances bronchial responsiveness in children. The mechanism for this effect and the possible role of atopy in it are unknown. The doses required to enhance bronchial responsiveness in children exposed to ETS are apparently much lower than those required to elicit similar effects among adult active smokers. A process of self-selection, by which adults who are more sensitive to the effects of tobacco smoke do not start smoking or quit smoking earlier, may explain this finding. Variations in bronchial responsiveness with age also may be involved (Hopp et al., 1985).

Increased bronchial responsiveness may be an important predisposing factor for the development of asthma in childhood (Hopp et al., 1990). Moreover, it has been suggested that bronchial hyperresponsiveness may have effects on the developing respiratory system that predispose to chronic obstructive lung disease in later life (O'Connor et al., 1989). Redline et al. (1989) examined bronchial responsiveness to hyperventilation with cold air and its association with growth of lung function over a 12-year period in 184 children and young adults (aged 8 to 23 years) over a maximum span of 12 years. Among subjects with persistent positive responses to cold air during followup, forced vital capacity grew faster, but forced expiratory flows grew more slowly, than among subjects who consistently did not respond to cold air. Among subjects with intermittently positive cold air responses, forced expiratory flows also grew more slowly than in controls, but growth of forced vital capacity was not changed. Although this study needs confirmation, its results suggest that bronchial hyperresponsiveness may have significant effects on the rate of growth of airway function and lung size in children.

7.2.5. ETS Exposure and Atopy

Atopy has been defined epidemiologically as the presence of immediate hypersensitivity to at least one potential allergen administered by skin prick test. Atopy is an immediate form of hypersensitivity to antigens (called allergens) that is mediated by IgE immunoglobulin. Allergy (as indicated by positive skin test reactivity to allergens, high levels of circulating IgE, or both) is known to be present in almost all cases of childhood asthma. Recent epidemiologic studies have indicated that an IgE-mediated reaction may be necessary for the occurrence of almost all cases of asthma at any age (Burrows et al., 1989).

Although genetic factors appear to play a major role in the regulation of IgE production (Meyers et al., 1987; Hanson et al., 1991), several reports have indicated that active smoking significantly increases total serum IgE concentrations and may thus influence the occurrence of allergy (Gerrard et al., 1980; Burrows et al., 1981; Zetterstrom et al., 1981; Taylor et al., 1985). Active smokers also have been found to have higher eosinophil counts and increased prevalence of eosinophilia when compared with nonsmokers (Kauffmann et al., 1986; Halonen et al., 1982; Taylor et al., 1985). The physical and chemical similarities between MS and ETS have prompted the investigation of a possible role of passive smoking in allergic sensitization in children.

Weiss and collaborators (1985) first reported a 2.2-fold increased risk of being atopic in children of smoking mothers. Martinez and coworkers (1988b) confirmed that children of smoking parents were significantly more likely to be atopic than were children of nonsmoking parents, and the researchers reported that this association was stronger for male children. They also found a rough dose-response relationship between the number of cigarettes smoked by parents and the intensity of the skin reactions to a battery of allergens. Ronchetti and collaborators (1990) extended these findings in the same population sample of Martinez and coworkers. They found that total serum IgE levels and eosinophil counts were significantly increased in children of smoking parents, and the effect was related to both maternal and paternal smoking.

It is relevant to note that, due to the so-called "healthy smoker effect," children of smokers should be genetically less sensitive than children of nonsmokers, because the latter are likely to include a disproportionate number of allergic subjects who are very sensitive to the irritant effects of smoke. As a consequence, the atopy-inducing effects of ETS may be substantially underestimated.

In summary, there is convincing evidence that both maternal smoking during pregnancy and postnatal exposure to ETS alter lung function and structure, increase bronchial responsiveness, and enhance the process of allergic sensitization. These changes elicited by exposure to tobacco products may predispose children to lower respiratory tract illnesses early in

life and to asthma, lower levels of lung function, and chronic airflow limitation later in life. Most of these same effects have been described for active smoking in adults. These smoke-induced changes are, therefore, known biological mechanisms for the increased prevalence of respiratory diseases associated with ETS exposure described later in this chapter.

Exposure to tobacco smoke products during pregnancy and to ETS soon after birth may be the most important preventable cause of early lung and airway damage leading to both lower respiratory illness in early childhood and chronic airflow limitation later in life.

7.3. EFFECT OF PASSIVE SMOKING ON ACUTE RESPIRATORY ILLNESSES IN CHILDREN

A review of the literature that examined the effects of exposure to ETS on the acute respiratory illness experiences of children was contained in the Surgeon General's report on the health consequences of involuntary smoking (U.S. DHHS, 1986) and in the report on environmental tobacco smoke by the NRC (1986). Table 7-1 shows the studies referenced in these two reports.

The Surgeon General's report concluded that "the results of these studies show excess acute respiratory illness in children of parents who smoke, particularly in children under 2 years of age," and that "this pattern is evident in studies conducted with different methodologies and in different locales" (page 44). It estimated that the increased risk of hospitalization for severe bronchitis or pneumonia ranged from 20% to 40% during the first year of life. The report stated that "young children appear to be a more susceptible population for the adverse effects of involuntary smoking than older children and adults" (page 44). Finally, the report suggested that "acute respiratory illnesses during childhood may have long-term effects on lung growth and development, and might increase the susceptibility to the effects of active smoking and to the development of chronic lung disease" (page 44).

The 1986 NRC report observed that "all the studies that have examined the incidence of respiratory illnesses in children under the age of 1 year have shown a positive association between such illnesses and exposure to ETS. The association is very unlikely to have arisen by chance" (page 208). It pointed out that "some of the studies have examined the possibility that the association is indirect by allowing for confounding factors . . . and have concluded that such factors do not explain the results. This argues, therefore, in favor of a causal explanation" (page 208). The report concluded that "bronchitis, pneumonia, and other lower-respiratory-tract illnesses occur up to twice as often during the first year of life in children who have one or more parents who smoke than in children of nonsmokers" (page 217).

Table 7-1. Studies on respiratory illness referenced in the Surgeon General's and National Research Council's reports of 1986

Study	No. of subjects	Age of subjects	Surgeon General	NRC
Cameron et al. (1969)	158	Children (6 to 9)	X	
Colley (1971)	2,205	Infants	X	
Colley (1974)	1,598	Children (6 to 14)		X
Dutau et al. (1981)	892	Infants/children (0 to 6)		X
Fergusson et al. (1981)	1,265	Infants	X	X
Leeder et al. (1976)	2,149	Infants	X	X
Pedreira et al. (1985)	1,144	Infants	X	X
Pullan and Hey (1982)	130	Children (10 to 11)	X	
Rantakallio (1978)	3,644	Infants/children (0 to 5)	X	X
Speizer et al. (1980)	8,120	Children (6 to 10)	X	X
Ware et al. (1984)	8,528	Children (5 to 9)	X	

7.3.1. Recent Studies on Acute Lower Respiratory Illnesses

Several recent studies not referenced in the Surgeon General's report or in the NRC report have addressed the relationship between parental smoking and acute lower respiratory illnesses in children (see Table 7-2).

Chen and coworkers (1986) studied 1,058 infants out of 1,163 infants born in a given period in two neighborhoods in Shanghai, People's Republic of China. Information on hospital admissions from birth to 18 months, smoking habits of household members, parental education, and social and living conditions was obtained by use of a self-administered questionnaire completed by the parents when the child reached 18 months of age. Hospital admissions were divided into those due to respiratory illness and those from all other conditions. None of the mothers in the study smoked. There was no statistically significant association between exposure to ETS and admission to the hospital for any condition other than respiratory illnesses. Compared with nonsmoking households, the risk of being admitted to a hospital for respiratory illnesses was 17% higher when one to nine cigarettes were smoked daily by household members (95% C.I. =

Table 7-2. Recent epidemiologic studies of effects of passive smoking on acute lower respiratory tract illnesses (LRIs)

Authors	Population studied	ETS exposure assessment	Outcome variable	Results[1]	Observations
Breese-Hall et al. (1984)	Cases: 29 infants hospitalized with bronchiolitis due to respiratory syncytial virus (RSV) Controls: 58 infants hospitalized for nonrespiratory conditions; 58 infants hospitalized due to LRIs not due to RSV	Parental questionnaire	See population studied	Cases vs. controls Odds ratio (OR) = 4.8 (1.8, 13.0) (>5 cig./day vs. none) LRI controls vs. non-LRI controls OR = 2.7 (1.3, 5.7)	Cases matched to controls for age, sex, race, month of admission, form of payment; selection bias not ruled out
Chen et al. (1986)	1,058 infants born in Shanghai, China	Parental self-administered questionnaire; number of cigarettes smoked by household members	Admissions to hospital for respiratory illness as reported by parents	Cig./day OR 1-9 1.2 (0.6, 2.3) >9 1.9 (1.1, 3.4)	Controlling for crowding, paternal education, feeding practices, birthweight, family history of chronic respiratory illness

(continued on the following page)

Table 7-2. (continued)

Authors	Population studied	ETS exposure assessment	Outcome variable	Results[1]	Observations
Chen et al. (1988)	2,227 infants born in Shanghai, China	Household self-administered questionnaire	Incidence of hospitalization for respiratory illness, incidence of bronchitis or pneumonia first 18 mo. of life	First 6 mo. of life: OR = 3.0 (1.6, 5.7); 7-18 mo. of life: OR = 1.8 (1.0, 3.2)	No smoking mothers; controlling for sex, birthweight, feeding practices, nursery care, paternal education, use of coal for cooking, family history of chronic respiratory illness
Chen (1989)	Same as above	Same as above	Same as above	First 18 mo. of life: incidence density ratio (IDR) = 1.6 for breast-fed babies; IDR = 3.4 for non-breast-fed babies; confidence intervals not calculable	

(continued on the following page)

Table 7-2. (continued)

Authors	Population studied	ETS exposure assessment	Outcome variable	Results[1]	Observations
McConnochie and Roghmann (1986a)	53 infants with bronchiolitis; 106 controls	Parental questionnaire at mean age 8 yr.	See population studied	Cases vs. controls OR = 2.4 (1.2, 4.8) (smoking mother vs. nonsmoking mother)	Cases matched to controls for sex and age; controlling for family history of asthma, social status, older siblings, crowding; selection bias not ruled out
Ogston et al. (1987)	1,565 infants in New Zealand	Maternal and paternal smoking habits during pregnancy by questionnaire	Upper and lower respiratory illnesses during first year of life	Paternal smoking OR = 1.43 (1.05, 1.96); maternal smoking OR = 1.82 (1.25, 3.64)	Upper and lower respiratory illnesses not distinguished; controlling for maternal age, feeding practices, heating type, social class
Anderson et al. (1988)	102 children hospitalized in Atlanta, Georgia, <2 yr.; 199 controls	Self-reported smoking habits of family members	LRI	No effect of parental smoking after controlling for other risk factors	Selection bias possible

(continued on the following page)

Table 7-2. (continued)

Authors	Population studied	ETS exposure assessment	Outcome variable	Results[1]	Observations
Woodward et al. (1990)	2,125 children aged 18 mo. to 3 yr.	Self-administered mailed questionnaire	"Respiratory score" regarding 13 different symptoms; top 20% compared with low 20%	OR = 2.0 (1.3, 3.4) of having a smoking mother for high scores compared with low scores; no effect of paternal smoking	Controlling for parental history of respiratory illness, child care, parental occupation, maternal stress
Wright et al. (1991)	847 white children born in Tucson, Arizona	Self-administered questionnaire and cotinine levels in a subsample	LRIs as assessed by the infants' pediatricians	OR = 1.5 (1.1, 2.2) of having smoking mother; no effect of paternal smoking	Effects significant only for LRIs occurring in the first 6 mo. of life; controlling for day care, room sharing, parental history of respiratory illnesses, feeding practices, sex, and maternal education
Reese et al. (1992)	491 children aged 1 mo. to 17 yr.	Cotinine levels in urine of children; questionnaire of parents' current smoking	Hospitalization for bronchiolitis	Higher levels in children hospitalized for bronchiolitis than in controls ($p<0.02$)	No effects of ETS on hospitalization for asthma

[1]95% confidence intervals in parentheses.

0.6, 2.3) and was 89% higher when more than nine cigarettes were smoked daily by household members (95% C.I. = 1.1, 3.4). The authors controlled for the effects of crowding, chronic respiratory illness in the family, father's education, type of feeding, and birthweight.

Chen and coworkers (1988) subsequently studied 2,227 out of 2,315 children born in the last quarter of 1983 in Chang-Ning District, Shanghai, People's Republic of China. There were no smoking mothers in this population. The authors reported a significant linear relationship of total daily cigarette consumption by family members with incidence density of hospitalization for respiratory illness and with cumulative incidence of bronchitis and pneumonia in the first 18 months of life. The relationship was stronger for the 1- to 6-month period than for the 7- to 18-month period: When compared with households whose members did not smoke at home, the risk of being hospitalized for respiratory illness during the 1- to 6-month interval was three times as high (95% C.I. = 1.6, 5.7) in households whose members smoked more than nine cigarettes at home, whereas comparison of the same two types of household showed that the risk of being hospitalized for respiratory illness during the 7- to 18-month interval was only 1.8 times as high (95% C.I. = 1.0, 3.2) in the smoking household. The relationship also was stronger among low-birthweight infants. Results were independent of sex, birthweight, feeding practices, nursery care, paternal education, family history of chronic respiratory diseases, and use of coal for cooking.

In a different publication based on the same data from the 1988 study, Chen (1989) reported that the effects of passive smoking were stronger in artificially fed infants than in breast-fed infants. When comparing breast-fed infants of nonsmoking and smoking families, the risk of being hospitalized for respiratory illness in the first 18 months of life was 1.6 times as high for breast-fed infants of smoking families (> 19 cig./day), whereas the same risk was 3.4 times as high among non-breast-fed infants of smoking families.

The studies by Chen (1989) and Chen and coworkers (1986, 1988) were retrospective in nature and thus not immune to possible biases generated by the fact that the occurrence of the outcome event may enhance reporting or recall of the conditions considered as risk factors. However, conclusions are strengthened by the finding that admissions for nonrespiratory illnesses were unrelated to passive smoking in the study in which the relationship was assessed (Chen et al., 1986) and by the fact that the finding remained significant after adjusting for known confounders.

Breese-Hall and coworkers (1984) studied 29 infants hospitalized with confirmed RSV bronchiolitis before age 2, 58 controls hospitalized for acute nonrespiratory conditions, and 58 controls hospitalized for acute lower respiratory illnesses from causes other than RSV. Cases and controls were matched for age, sex, race, month of admission, and form of payment for

hospitalization. Information on smoking habits in the family was obtained at the time of each patient's admission. Cases were 4.8 times as likely as controls (95% C.I. = 1.8, 13.0) to have one or more household members who smoked five or more cigarettes per day. However, there was no significant difference in the prevalence of cigarette smoking in the households of subjects with respiratory illnesses caused by RSV and those not caused by RSV. This was attributable to the fact that the controls with respiratory illnesses not caused by RSV were also much more likely to live with smokers of five or more cigarettes per day than were controls with nonrespiratory illnesses (OR = 2.7, 95% C.I. = 1.3, 5.7). Little information is given about enrollment and refusals; thus, it is not possible to know if selection bias may have influenced the results. Also, other possible confounders such as socioeconomic level were not taken into account when matching cases to controls or when data were analyzed.

McConnochie and Roghmann (1986a) compared 53 infants drawn from the patient population of a group practice in Rochester, New York, who had physician-diagnosed bronchiolitis before age 2 years, with 106 controls from the same practice who did not have lower respiratory illnesses during the first 2 years of life and who were matched with cases for sex and age. Parental interviews were conducted when the child had a mean age of 8.4 years. Parents were asked about family history of respiratory conditions and allergy, socioeconomic status, passive smoking, home cooking fuel, home heating methods, and household pets. Passive smoking was defined as current and former smoking of "at least 20 packs of cigarettes or 12 ounces of tobacco while living in the home with the subject." Current and former smoking was scored equally, based on the assumption that the report of either reflected passive smoking in the first 2 years of life. Frequency of paternal smoking was not increased among children who had bronchiolitis. Cases were 2.4 times (95% C.I. = 1.2, 4.8) as likely to have smoking mothers as were controls. The association was stronger in families with older siblings (OR = 8.9); however, a multiplicative test for this interaction did not reach statistical significance. The authors studied 63% of eligible cases and 34% of eligible controls. Although the reasons for exclusion from both groups are detailed, selection bias cannot be excluded completely, and the authors give no information about maternal smoking habits among excluded subjects. Also, overreporting of smoking by parents who were aware of their child's history of bronchiolitis may have introduced biases due to differential misclassification. However, the results were consistent across groups classified according to family history of asthma or allergy, social status, presence of older siblings, and crowding.

Ogston and coworkers (1987) conducted a prospective study of 1,565 infants of primigravidae enrolled antenatally in the Tayside Morbidity and Mortality Study in New Zealand. Information on the father's smoking habits and on the mother's smoking habits during pregnancy

was obtained at the first antenatal interview and from a postnatal questionnaire. A summary record was completed when the child was 1 year of age and included a report of the child's respiratory illnesses (defined as "infections of the upper or lower respiratory tract") during the first year of life derived from observations made by health visitors during scheduled visits to see the child. The authors used a multiple logistic regression to control for the possible effects of maternal age, feeding practices, heating type, and father's social class on the relationship between parental smoking and child health. Of the 588 children of nonsmokers in this sample, 146 (24.8%) had respiratory illnesses during the first year of life. Paternal smoking was associated with a 43% increase (95% C.I. = 4.7, 96.1) in the risk of having respiratory illnesses in the first year of life, and this was independent of maternal smoking. The risk of having a respiratory illness was 82% higher (95% C.I. = 25.6, 264.4) in infants of smoking mothers than in infants of nonsmoking parents. Smoking by both parents did not increase the risk of having respiratory illnesses beyond the level observed in infants with smoking mothers and nonsmoking fathers. It is difficult to compare this study with other reports on the same issue because the authors could not distinguish between upper and lower respiratory tract illnesses.

Anderson and coworkers (1988) performed a case-control study of 102 infants and young children hospitalized in Atlanta, Georgia, for lower respiratory tract illnesses before age 2 and 199 age- and sex-matched controls. The unadjusted relative odds of having any family member smoking cigarettes were 2.0 times as high ($p < 0.05$) among cases as among controls (confidence interval was not calculable from the reported data). The effect disappeared, however, after controlling for other factors (prematurity, history of allergy in the child, feeding practices, number of persons sleeping in the same room with the child, immunization of the child in the last month) in a multivariable logistic regression analysis. No information is provided in this report about maternal and paternal smoking separately, and the number of cigarettes smoked at home by each family member was not recorded either. Also, almost 30% of all target cases declined participation in the study, and no information was available on smoking habits in the families of these children. No information is given about number of refusals among controls.

Woodward and collaborators (1990) obtained information about the history of acute respiratory illnesses in the previous 12 months on 2,125 children aged 18 months to 3 years whose parents answered a questionnaire mailed to 4,985 eligible families in Adelaide, Australia. A "respiratory score" was calculated from responses to questions regarding 13 different upper and lower respiratory illnesses. A total of 1,218 parents (57%) gave further consent for a home interview. From this total, parents of 258 cases (children whose respiratory score fell in the top 20% of scores) and 231 "controls" (children whose scores were within the bottom 20% of scores) were interviewed at home. When compared with controls, cases were twice as likely to have a

mother who smoked during the first year of life (95% C.I. = 1.3, 3.4). This effect was independent of parental history of respiratory illnesses, other smokers in the home, use of group child care, parental occupation, and level of maternal stress and social support. The authors found no differences in the way smokers and nonsmokers perceived or managed acute respiratory illnesses in their children. Based on this finding, they ruled out that such differences could explain their findings. They also reported that feeding practices strongly modified the effect of maternal smoking; among breast-fed infants, cases were 1.8 times as likely to have smoking mothers as were controls (95% C.I. = 1.2, 2.8), whereas among non-breast-fed infants, cases were 11.5 times as likely to have smoking mothers as were controls (95% C.I. = 3.4, 38.5).

Wright and collaborators (1991) studied the relationship between parental smoking and incidence of lower respiratory tract illnesses in the first year of life in a cohort of 847 white non-Hispanic infants from Tucson, Arizona, who were enrolled at birth and followed prospectively. Lower respiratory illnesses were diagnosed by the infants' pediatricians. Maternal and paternal smoking was ascertained by questionnaire. For verification of smoking habits, the researchers measured cotinine in umbilical cord serum of a sample of 133 newborns who were representative of the population as a whole. Cotinine was detectable in umbilical cord sera of all infants whose mothers reported smoking during pregnancy and in 7 of 100 cord specimens of infants whose mothers said they had not smoked during pregnancy. There was a strong relationship between cotinine level at birth and the amount that the mother reported having smoked during pregnancy.

Children whose fathers smoked were no more likely to have a lower respiratory tract illness in the first year of life than were children of nonsmoking fathers (31.3% vs. 32.2%, respectively). The incidence of lower respiratory tract illnesses was 1.5 times higher (95% C.I. = 1.1, 2.2) in infants whose mothers smoked as in infants whose mothers were nonsmokers. This relationship became stronger when mothers who were heavy smokers were separated from light smokers; 45.0% of children born to mothers who smoked more than 20 cigarettes per day had a lower respiratory illness, compared with 32.1% of children whose mothers smoked 1 to 19 cigarettes per day and 30.5% of children of nonsmoking mothers ($p < 0.05$). The authors tried to differentiate the effects of maternal smoking during pregnancy from those of postnatal exposure to ETS but concluded that the amount smoked contributed more to lower respiratory tract illness rates than did the time of exposure. The authors also found that maternal smoking had a significant effect on the incidence of lower respiratory tract illnesses only for the first 6 months of life; the risk of having a first lower respiratory illness between 6 and 12 months was independent of maternal smoking habits. A logistic regression showed that the effect of maternal smoking was independent of parental childhood respiratory troubles, season of birth, day-care

use, and room sharing. Feeding practices, maternal education, and child's gender were unrelated to incidence of lower respiratory illnesses in this sample and were not included in the regression. The analysis also showed a significant interaction between maternal smoking and day-care use; the effects of maternal smoking were significant when the child did not use day care (OR = 2.7; 95% C.I. = 1.2, 5.8) but were weaker and did not reach significance among infants who used day care (OR = 1.9; 95% C.I. = 0.9, 4.0). The authors suggested that day-care use may protect against lower respiratory illnesses by reducing exposure to ETS.

Reese et al. (1992) studied urinary cotinine levels in 491 children, aged 1 month to 17 years, on admission to hospital. Children admitted for bronchiolitis had higher urinary cotinine levels than a group of children of similar age admitted for nonrespiratory illnesses ($p < 0.02$). The researchers concluded that there are objective data linking passive smoking to hospital admission for bronchiolitis in infants.

7.3.2. Summary and Discussion on Acute Respiratory Illnesses

Both the literature referenced in the Surgeon General's report (U.S. DHHS, 1986) and the NRC report (1986) and the additional, more recent studies considered in this report provide strong evidence that children who are exposed to ETS in their home environment are at considerably higher risk of having acute lower respiratory tract illnesses than are unexposed children. Increased risk associated with ETS exposure has been found in different locales, using different methodologies, and in both inpatient and outpatient settings. The effects are biologically plausible (see Section 7.2). Several studies also have reported a dose-response relationship between degree of exposure (as measured by number of cigarettes smoked in the household) and risk of acute respiratory illnesses. This also supports the existence of a causal explanation for the association.

The majority of studies found that the effect was stronger among children whose mothers smoked than among those whose fathers smoked. This is further evidence in favor of a causal explanation, because infants are generally in closer and more frequent contact with their mothers. There are now also fairly convincing data showing that the increased incidence of acute respiratory illnesses cannot be attributed exclusively to in utero exposure to maternal smoke. In fact, Chen (1989) and Chen and coworkers (1986, 1988) reported increased risk of acute respiratory illnesses in Chinese children living with smoking fathers and in the total absence of smoking mothers. This effect also could be attributed either to in utero exposure to the father's smoke or to an effect on the father's sperm. This seems unlikely, however, because no such effects of parental smoking during pregnancy have been described in similar studies performed in Western countries. Furthermore, Woodward and coworkers (1990) found that children of smoking mothers were significantly more prone to acute respiratory illnesses even after mothers who

smoked during pregnancy were excluded from the analysis. This clearly suggests the existence of direct effects of ETS exposure on the young child's respiratory health that are independent of in utero exposure to tobacco smoke products.

There is also convincing evidence that the risk is inversely correlated with age; infants aged 3 months or less are reported to be 3.3 times more likely to have lower respiratory illnesses if their mothers smoke 20 or more cigarettes per day than are infants of nonsmoking mothers (Wright et al., 1991). Increases in incidence of 50% to 100% (relative risks of 1.5-2.0) have been reported in older infants and young children. The evidence for an effect of ETS is less persuasive for school-age children, although trends go in the same direction as those reported for younger children. This may be due to a decrease in illness frequency, to physiological development of the respiratory tract or immune system with age, or to a decreased contact between mother and child with age.

Reasonable attempts have been made in most studies to adjust for a wide spectrum of possible confounders. The analyses indicate that the effects are independent of race, parental respiratory symptoms, presence of other siblings, socioeconomic status or parental education, crowding, maternal age, child's sex, and source of energy for cooking. One study (Graham et al., 1990) also showed that the effect of ETS exposure on proneness to acute respiratory illnesses in infancy and early childhood was also independent of several indices of maternal stress, lack of maternal social support, and family dysfunction. Other factors, such as breastfeeding, decreased birthweight, and day-care attendance, have been shown to modify the risk.

Some sources of bias may have influenced the results, but it is highly unlikely that they explain the consistent association between acute lower respiratory illness and ETS exposure. With one exception (Wright et al., 1991), all studies relied exclusively on questionnaires or interviews to assess exposure. Although questions tend to be very specific, overreporting or more accurate reporting of smoking habits by parents of affected children is possible, particularly in case-control and retrospective studies. However, such a bias should affect both respiratory and nonrespiratory outcomes, and at least two studies have shown no association between nonrespiratory outcomes and ETS exposure (Chen et al., 1988; Breese-Hall et al., 1984). Selection bias could not be excluded in some case-control studies, but satisfactory efforts were made to avoid this source of bias in most studies.

7.4. PASSIVE SMOKING AND ACUTE AND CHRONIC MIDDLE EAR DISEASES

The Surgeon General's report (U.S. DHHS, 1986) and the NRC report (1986) reviewed five studies demonstrating an excess of chronic middle ear disease in children exposed to parental cigarette smoke (Table 7-3). Both reports conclude that the data are consistent with increased rates of chronic ear infections and middle ear effusions in children exposed to ETS at home.

Table 7-3. Studies on middle ear diseases referenced in the Surgeon General's report of 1986

Study	No. of subjects	Age of subjects (years)
Said et al. (1978)	3,290	10-20
Iversen et al. (1985)	337	0-7
Kraemer et al. (1983)	76	Young children (unspecified age)
Black (1985)	450	4-9
Pukander et al. (1985)	264	2-3

7.4.1. Recent Studies on Acute and Chronic Middle Ear Diseases

Several recent studies not referenced in the Surgeon General's report or in the NRC report have addressed the relationship between parental smoking and middle ear illnesses in children (Table 7-4).

Fleming and coworkers (1987) examined retrospectively risk factors for the acquisition of infections of the upper respiratory tract in 575 children less than 5 years of age. Information on smoking habits and on upper respiratory tract infections and ear infections in the 2 weeks prior to interview was obtained from the children's guardians. The authors reported a 1.7-fold increase ($p = 0.01$) in the risk of having an upper respiratory illness in children of smoking mothers when compared with children of nonsmoking mothers. This effect was independent of feeding practices, family income, crowding, day-care attendance, number of siblings aged less than 5 years, child's age, and race. The authors calculated that 10% of all upper respiratory illnesses in the population were attributable to maternal smoking, a proportion that was comparable with that attributable to day-care attendance. There was no relationship between maternal smoking and frequency of ear infections in this population sample.

Willatt (1986) studied 93 children who were the entire group of children admitted to a Liverpool hospital for tonsillectomy (considered an index of frequent upper respiratory or ear infections) during a 3-month period and 61 age- and sex-matched controls. The median age was 6.9 years (range 1.8-14.9). Parents were asked about the number of sore throats in the previous 3 months and the smoking habits of all members of the household. There was a significant

Table 7-4. Recent epidemiologic studies of effects of passive smoking on acute and chronic middle ear diseases

Authors	Population studied	ETS exposure assessment	Outcome variable	Results[1]	Observations
Willatt (1986)	93 children aged 2-15 yr. admitted to hospital for tonsillectomy; 61 age- and sex-matched controls	Questionnaire answered by parents	Tonsillectomy	OR = 2.1 (1.1, 4.0) of having smoking mothers	Controlling for birthweight, sex, age, feeding practices, social class, crowding, sore throats in other household members
Fleming et al. (1987)	575 children <5 yr.	Questionnaire answered by child's guardian	Upper respiratory illnesses (URI) and infections in previous 2 weeks	OR = 1.7 for URI when mother smoked; no effect on ear infection	Controlling for feeding practices, income, crowding, day care, siblings, sex, race
Tainio et al. (1988)	198 Finnish newborns followed from birth to age 2.3 yr.	Questionnaire to parents	Recurrent otitis media as diagnosed by pediatricians	No effects	No distinction between maternal and paternal smoking; small sample

(continued on the following page)

Table 7-4. (continued)

Authors	Population studied	ETS exposure assessment	Outcome variable	Results[1]	Observations
Reed and Lutz (1988)	24 cases of acute otitis media; 25 controls	Questionnaire to parents	Abnormal tympanometry	OR = 4.9 (1.4, 17.2) of having smokers at home	Small sample; selection bias cannot be ruled out
Hinton (1989)	115 children aged 1-12 yr. admitted for grommet insertion; 36 controls aged 2-11 yr. in Great Britain	Questionnaire to parents	Being admitted for grommet insertion	OR = 2.1 (1.0, 4.5) of having smoking parents	No control for confounders; selection bias not ruled out
Teele et al. (1989)	877 children observed for 1 yr.; 698 observed for 3 yr.; 498 observed for 7 yr. in Boston, Massachusetts	Questionnaire to parents	Acute otitis media; number of days with middle ear effusion	13% more acute otitis during first yr. of life; more days with middle ear effusion ($p<0.009$) only during first yr.; no effects after controlling for confounders	No distinction between paternal and maternal smoking; parents smoking 1 cig./day included among smokers
Corbo et al. (1989)	1,615 children aged 6-13 yr. in Abruzzo, Italy	Questionnaire to parents	Child's snoring as reported by parents	OR = 1.8 (1.1, 3.0) for moderate smokers (1-19 cig./day); OR = 1.9 (1.2, 3.1) for heavy smokers (≥20 cig./day)	No distinction between maternal and paternal smoking

(continued on the following page)

Table 7-4. (continued)

Authors	Population studied	ETS exposure assessment	Outcome variable	Results[1]	Observations
Strachan et al. (1989)	736 children in third elementary class in Edinburgh, Scotland	Salivary cotinine level	Prevalence of middle ear effusion as assessed by tympanogram	OR for doubling salivary cotinine = 1.14 (1.03, 1.27)	One-third of cases of middle ear effusion attributable to passive smoking; controlling for sex, housing tenure, social class, crowding, gas cooking, damp walls
Takasaka (1990)	77 children aged 4-8 yr. with otitis media with effusion; 134 controls matched for age and sex in Sendai, Japan	Questionnaire to parents	See population studied	No effect	Low power
Etzel et al. (1992)	132 children from day-care facility aged <3 yr.	Serum cotinine levels	Otitis media with effusion	Incidence density ratio 1.4 (1.2, 1.6) for exposed children; increases significant for ages ≤2 years only	8% of cases attributable to ETS exposure

[1]95% confidence intervals in parentheses.

relationship ($p < 0.05$) between number of episodes of sore throat and number of cigarettes smoked by the mother. The effect was independent of birthweight, sex, child's age, feeding practices, social class, crowding, and number of sore throats and tonsillectomies in other household members. The relative odds of having a smoking mother were 2.1 times as high (95% C.I. = 1.1, 4.0) in children about to undergo tonsillectomy as in children not undergoing tonsillectomy.

Tainio and coworkers (1988) followed 198 healthy newborns from birth to 2.3 years of age. The investigators recorded physician-diagnosed recurrent otitis media (defined as more than four episodes of otitis media during the first 2 years or more than four episodes during the second year). Parental smoking was more frequent (55%) among the infants with recurrent otitis media than in the comparison group (33%; $p < 0.05$). The authors comment, however, that "parental smoking was not a risk factor for recurrent otitis media," probably because there was no significant relationship between parental smoking and recurrent otitis media using definitions of the latter that differed from the one described above. No distinction was made in this study between the possible effects of maternal and paternal smoking. In addition, the study sample was probably too small to obtain reliable risk calculations.

Reed and Lutz (1988) studied 24 of 70 eligible children who had been seen in a family practice office for acute otitis media during a period of 4 months and 25 of 70 eligible children who had been seen for other reasons. Forty-five of these children had tympanograms performed and had information on household smoke exposure. Prevalence of an abnormal tympanogram (indicating the presence of middle ear effusion) was higher among children exposed to smokers at home (OR = 4.86, 95% C.I. = 1.4, 17.2). Results were independent of feeding practices, history of upper respiratory illness in the past month, low socioeconomic status, sex, age, and attendance at a day-care center. Only a small fraction of eligible subjects were included in this study, and the possibility of selection bias as an explanation for the reported results cannot be ruled out.

Hinton (1989) compared 115 children aged 1 to 12 years (mean = 5 years) admitted to a British hospital for grommet insertion with 36 children aged 2 to 11 years (mean = 6 years) with normal ears who were taken from an orthoptic clinic. Prevalence of smoking was significantly higher in parents of cases than in parents of controls (OR = 2.1, 95% C.I. = 1.0, 4.5). Potential sources of selection bias or selective misclassification cannot be determined from the data reported by the author. No effort was made to control for possible confounders.

Teele and coworkers (1989) studied consecutively enrolled children being followed in two health centers in Boston from shortly after birth until 7 years of age. Acute otitis media and middle ear effusion were diagnosed by the children's pediatricians. Data were analyzed for 877 children observed for at least 1 year, 698 children observed for at least 3 years, and 498 children

observed until 7 years of age. A history of parental smoking was obtained when each child became 2 years old. A parent was considered a smoker if he or she smoked more than one cigarette per day. The child was considered exposed if either parent was a smoker. The authors reported that the incidence of acute otitis media during the first year of life was 13% higher in children of smoking parents when compared with children of nonsmoking parents ($p < 0.05$), but statistical significance was no longer present after controlling for alleged confounders (site of health care, season of birth, birthweight, socioeconomic status, presence and number of siblings, room sharing, feeding practices, and sibling or parental history of ear infection and allergic diseases). Several of these variables may not have been confounders if they were not related to both parental smoking and incidence of acute otitis media. Controlling for risk factors that are not confounders may result in overcorrection. Parental smoking was not associated with an increased risk for acute otitis media during the first 3 years or 7 years of life. Likewise, parental smoking was associated with a significant increase in the number of days with middle ear effusion, but only during the first year of life ($p < 0.009$), and the effect was no longer present after alleged confounders were controlled for. The authors do not provide information on separate risks for maternal and paternal smoking or on the incidence of acute otitis media and middle ear effusion in children of heavy smokers.

Takasaka (1990) performed a case-control study on 201 children aged 4 to 8 in Sendai, Japan. Sixty-seven subjects had otitis media with effusion, and the remaining 134 children were a control group matched to cases by age, sex, and kindergarten class. The investigators found no significant differences in prevalence of exposure to two or more household cigarette smokers between children with and without otitis media with effusion (no information on either odds ratios or C.I.s was given). The power of this study may have been too low to determine risk factors for middle ear effusions reliably.

Corbo and coworkers (1989) examined 1,615 children aged 6 to 13 years who shared a bedroom with siblings or parents in Abruzzo, Italy. Parents were asked if the child snored and the frequency of snoring. Parents were asked about their own smoking habits; they were considered moderate smokers if the summed total for both parents was fewer than 20 cigarettes per day and heavy smokers if the summed total was 20 or more cigarettes per day. Prevalence of habitual snoring in children increased slightly with the amount of cigarettes smoked by parents; children of heavy smokers were 1.9 times as likely to be habitual snorers as children in nonsmoking households (95% C.I. = 1.2, 3.1), whereas children of moderate smokers were 1.8 times as likely to be habitual snorers as children of nonsmoking parents (95% C.I. = 1.1, 3.0). Habitual snorers were more likely to have had a tonsillectomy, but only if their parents smoked. The authors suggested

that these results are plausible because adult smokers are also at increased risk of being habitual snorers.

Strachan and collaborators (1989) performed tympanograms and collected saliva for cotinine determinations in 736 children in the third primary class (ages 6½ to 7½ years) in Edinburgh, Scotland. Median of salivary cotinine concentrations was 0.19 ng/mL for 405 subjects living with no smoker, 1.8 ng/mL for 241 subjects living with one smoker, and 4.4 ng/mL for 124 subjects living with two or more smokers. For a given number of smokers in the household, girls had higher cotinine levels than boys, and children living in rented houses (i.e., of lower socioeconomic level) had higher cotinine levels than children living in houses owned by their parents. The authors found a linear relation between the logarithm of the salivary cotinine concentration and the prevalence of middle ear effusion. The authors calculated odds ratios for abnormal tympanometry relative to children with undetectable cotinine concentrations, after adjustment for sex, housing tenure (rented or owned), social class, crowding, gas cooking, and the presence of damp walls. The odds ratio for a doubling of salivary cotinine concentration was 1.14 (95% C.I. = 1.03, 1.27). At a salivary cotinine concentration of 1 ng/mL, the odds ratio of having an abnormal tympanogram was 1.7, whereas an odds ratio of 2.3 was calculated for a cotinine level of 5 ng/mL. At least one-third of all cases of middle ear effusion may have been attributable to passive smoking.

Etzel and coworkers (1992) studied 132 children who attended a day-care facility during the first 3 years of life. The investigators measured serum cotinine levels and considered a level of 2.5 ng/mL or more to be indicative of exposure to tobacco smoke. The 87 children with serum cotinine above this level had a significantly (38%) higher rate of new episodes of otitis media with effusion during the first 3 years of life than the 45 children with lower or undetectable levels (incidence density ratio = 1.4, 95% C.I. = 1.2, 1.6). The authors calculated that 8% of the cases of otitis media with effusion occurring in this population were attributable to exposure to tobacco smoke.

7.4.2. Summary and Discussion of Middle Ear Diseases

There is some evidence suggesting that the incidence of acute upper respiratory tract illnesses and acute middle ear infections may be more common in children exposed to ETS. However, several studies have failed to find any effect. In addition, the possible role of confounding factors, the lack of studies showing clear dose-response relationships, and the absence of a plausible biological mechanism preclude more definitive conclusions.

Available data provide good evidence demonstrating a significant increase in the prevalence of middle ear effusion in children exposed to ETS. Several studies in which no

significant association was found between ETS exposure and middle ear effusion were not specifically designed to test this relationship, and, therefore, either power was insufficient or assessment of the degree of exposure was inadequate. Also, Iversen and coworkers (1985), who assessed middle ear effusion objectively, suggested that the risk associated with passive smoking increased with age. This may explain the negative results of several studies based on preschool children; the sample sizes of these studies may have been inadequate to test for increased risks of 50% or less, as would be expected in children under 6 years of age. The finding of a log-linear dose-response relationship between salivary cotinine levels and the prevalence of abnormal tympanometry in one study (Strachan et al., 1989) adds to the evidence favoring a causal link. Although not all studies adjusted for possible confounders and selection bias cannot be excluded in the case-control studies reviewed, the evidence as a whole suggests that the association is not likely to be due to chance, bias, or factors related to both ETS exposure and middle ear effusion.

The biological mechanisms explaining the association between ETS exposure and middle ear effusion require further elucidation. Otitis media with effusion is usually attributed to a loss of patency of the eustachian tube, which may be enhanced by upper respiratory infection, impaired mucociliary function, or anatomic factors (Strachan et al., 1989). It is possible that pharyngeal narrowing by adenoidal tissue (and, consequently, eustachian tube dysfunction) may be more common in these children. This is suggested by reports of a higher prevalence of maternal smoking among children about to undergo or who have undergone tonsillectomy and by an increased prevalence of habitual snoring among children of smoking parents. Impaired mucociliary clearance has been demonstrated convincingly in smoking adults (U.S. DHHS, 1984). No data are available on mucociliary transport in children exposed to ETS. However, ETS may affect mucociliary clearance in children as in adults. If this were the case and if normal mucociliary clearance is required for rapid resolution of otitis media, exposure to ETS could result in increased prevalence of chronic middle ear effusion.

The increased prevalence of middle ear effusion attributable to ETS exposure has very important public health consequences. Middle ear effusion is the most common reason for hospitalization of young children for an operation and thus imposes a heavy financial burden to the health care system (Black, 1984). There is also evidence suggesting that hearing loss associated with middle ear effusion may have long-term consequences on linguistic and cognitive development (Maran and Wilson, 1986).

7.5. EFFECT OF PASSIVE SMOKING ON COUGH, PHLEGM, AND WHEEZING

Studies addressing the effects of passive smoking on frequency of chronic cough, phlegm, and wheezing were reviewed both in the Surgeon General's report (U.S. DHHS, 1986) and in the report by the NRC (1986) (see Table 7-5).

The Surgeon General's report concluded that children whose parents smoke were found to have 30% to 80% excess prevalence of chronic cough or phlegm compared with children of nonsmoking parents. For wheezing, the increase in risk varied from none to over sixfold among the studies reviewed. The report noted that the association with parental smoking was not statistically significant for all symptoms in all studies, but added that the majority of studies showed an increase in symptom prevalence with an increase in the number of smoking household members in the home. The report stated that the results of some studies could have been confounded by the child's own smoking habits, but noted that many studies showed a positive association between parental smoking and symptoms in children at ages before significant experimentation with cigarettes is prevalent. The report concluded that "chronic cough and phlegm are more frequent in children whose parents smoke compared to nonsmokers. The implications of chronic respiratory symptoms for respiratory health as an adult are unknown and deserve further study" (page 107).

The NRC report concluded that "children of parents who smoke compared with children of parents who do not smoke show increased prevalence of respiratory symptoms, usually cough sputum and wheezing. The odds ratios for the larger studies, adjusted for the presence of parental symptoms, were 1.2-1.8, depending on the symptoms. These findings imply that ETS exposures cause respiratory symptoms in some children" (page 216).

7.5.1. Recent Studies on the Effect of Passive Smoking on Cough, Phlegm, and Wheezing

Several recent studies not considered either in the NRC report (1986) or in the Surgeon General's report (U.S. DHHS, 1986) have addressed the relationship between passive smoking and respiratory symptoms in children (Table 7-6).

McConnochie and Roghmann (1986b) studied 223 of 276 eligible children aged 6 to 10 years without a history of bronchiolitis who were drawn from the patient population of a group practice in Rochester, New York. Information regarding the child's history of wheezing in the previous 2 years, socioeconomic status, family history of respiratory illnesses, and smoking in the household was obtained by questionnaire. Information on breastfeeding was obtained by record checks and interviews. Children whose mothers smoked were more likely to be current wheezers than were children whose mothers did not smoke (OR = 2.2, 95% C.I. = 1.0, 4.8). Neither paternal

Table 7-5. Studies on chronic respiratory symptoms referenced in the Surgeon General's and National Research Council's reports of 1986

Study	No. of subjects	Age of subjects	Respiratory symptoms	Surgeon General	NRC
Bland et al. (1978)	3,105	Children/adol. (12-13)	Cough	X	X
Charlton (1984)	15,000	Children/adol. (8-19)	Cough	X	
Colley et al. (1974)	2,426	Children (6-14)	Cough	X	X
Dodge (1982)	628	Children (8-10)	Wheeze, phlegm, cough	X	X
Ekwo et al. (1983)	1,355	Children (6-12)	Cough, wheeze	X	
Kasuga et al. (1979)	1,937	Children (6-11)	Wheeze, asthma	X	
Lebowitz and Burrows (1976)	1,525	Children (<15)	Cough, phlegm, wheeze	X	X
Schenker et al. (1983)	4,071	Children (5-14)	Cough, phlegm, wheeze	X	X
Schilling et al. (1977)	816	Children/adol. (7-16)	Cough, phlegm, wheeze	X	X
Tager et al. (1979)	444	Children/adol. (5-19)	Cough, wheeze		X
Ware et al. (1984)	10,106	Children (6-13)	Cough, wheeze, phlegm		X
Weiss et al. (1980)	650	Children (5-9)	Cough, phlegm, wheeze	X	X

Table 7-6. Recent epidemiologic studies of effects of passive smoking on cough, phlegm, and wheezing

Authors	Population studied	ETS exposure assessment	Outcome variable	Results[1]	Observations
McConnochie and Roghmann (1986b)	223 children aged 6 to 10 yr. in Rochester, New York	Parental questionnaire	Wheezing in the previous 2 yr.	OR = 2.2 (1.0, 4.8) for maternal smoking; no effect of paternal smoking	Effect disappeared after controlling for confounders; strong interaction between smoking and family history of allergy (OR = 4.5 [1.7, 12.0])
Park and Kim (1986)	3,651 children aged 0 to 14 yr. in South Korea	Questionnaire to household members	Cough in the 3 mo. prior to interview	OR = 2.4 (1.4, 4.3) for families smoking 1 to 14 cig./day; OR = 3.2 (1.9, 5.5) for families smoking ≥15 cig./day	Results only significant among families whose adult members did not have chronic cough

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Table 7-6. (continued)

Authors	Population studied	ETS exposure assessment	Outcome variable	Results[1]	Observations
Bisgaard et al. (1987)	5,953 infants enrolled at birth in Denmark	Maternal questionnaire	Episodes of wheeze during first yr. of life	OR = 2.7 (1.8, 4.0) for children whose mothers smoked ≥3 cig./day	Controlling for social status and sex; almost one-third of original sample did not participate in the study
Geller-Bernstein et al. (1987)	80 children aged 6 to 24 mo. in Israel	Parental questionnaire	Persistent wheeze as assessed by physician after 1½ yr. of followup	OR = 3.1 (1.1, 8.9) for having smoking parents	No control for parental symptoms
Cogswell et al. (1987)	100 infants of allergic parents enrolled at birth; 73 still followed at age 5 yr.	Parental questionnaire	Number of subjects who developed wheezing at different times after birth	By 5 yr., 63% of parents who smoked had wheezing children, compared with 37% of nonsmoking parents ($p<0.05$)	> one-fourth of subjects lost to followup
Toyoshima et al. (1987)	48 wheezy children <3 yr. followed in Osaka, Japan	Parental questionnaire	Number of children still wheezing at end of followup	OR = 11.8 (1.3, 105.0) for children living in smoking households	Selection bias cannot be ruled out
Tsimoyianis et al. (1987)	193 12- to 17-year-old high school athletes	Questionnaire to the child on household smoking habits	Self-report of cough, bronchitis, wheeze, and shortness of breath	No effect on bronchitis, wheeze, shortness of breath. Increased frequency of cough ($p=0.08$)	Reporting bias cannot be ruled out

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Table 7-6. (continued)

Authors	Population studied	ETS exposure assessment	Outcome variable	Results[1]	Observations
Andrae et al. (1988)	4,990 children aged 6 mo. to 16 yr. in Norrkoping, Sweden	Self-report of smoking by parents	Exercise-induced cough as reported by parents	OR = 1.4 (1.1, 1.8) for children whose parents smoked	No effort made to control for active smoking in older children
Somerville et al. (1988)	7,144 children aged 5 to 11 yr. in England and Scotland; 134 controls matched for age and sex in Sendai, Japan	Questionnaire answered by child's mother	Parental reports of respiratory symptoms in the child	Among English children whose parents smoked ≥20 cig./day OR = 1.6 (1.2, 2.2) of having "wheezy chest most nights"	
Rylander et al. (1988)	67 children aged 4 to 7 yr. hospitalized with respiratory syncytial virus bronchiolitis in Stockholm, Sweden	Parental questionnaire	Subsequent occasional and recurrent wheezing	Occasional wheezing OR = 4.3 (1.1, 16.4) in children of smoking parents; no effect on recurrent wheezing	Small number of subjects
Strachan (1988)	1,012 schoolchildren 6.5 to 7.5 yr. old in Edinburgh, Scotland	Parental questionnaire	Respiratory symptoms in children	No effect on wheeze; cough at night, OR = 1.6 (1.1, 2.6) in children living with one smoker; OR = 2.5 in children living with two smokers	

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Table 7-6. (continued)

Authors	Population studied	ETS exposure assessment	Outcome variable	Results[1]	Observations
Lewis et al. (1989)	60 cases of chronic cough aged <6 yr.; 60 controls; in Salford, United Kingdom	Parental questionnaire	See population studied	OR = 1.7 (0.8, 3.5) in children living with a smoker	Low power
Neuspiel et al. (1989)	9,670 children enrolled at birth in Great Britain	Parental questionnaire at birth, at age 5 yr. and at age 10 yr.	Wheeze between ages 1 and 10 yr.	Cumulative incidence: 5.2% mother non-smoker, 6.6% mother smoked 1 to 4 cig./day, 7.5% mother smoked 5 to 11 cig./day, 8.1% mother smoked 15 to 24 cig./day, 8.9% mother smoked >24 cig./day	Independent of sex, allergy, smoking during pregnancy, paternal smoking, crowding, dampness, feeding practices, gas cooking, social status, and maternal respiratory symptoms
Chan et al. (1989a)	134 children 7 yr. of age in London, England, <2,000 g birthweight; 123 controls with normal birthweight	Parental questionnaire	Wheeze and cough	OR = 2.7 (1.3, 5.5) of having wheeze at age 7 in children of smoking mothers, OR = 2.4 (1.3, 4.6) of having cough	Effects on wheeze independent of confounders; effects on cough disappeared after controlling for confounders

[1]95% confidence intervals in parentheses.

smoking nor total household smoking had any influence on the prevalence of wheezing. When the authors controlled for family history of respiratory allergy, direct effects of maternal smoking on prevalence of wheezing failed to reach statistical significance. However, there was a strong association between maternal smoking and wheezing among children with a positive family history of respiratory allergy (OR = 4.5, 95% C.I. = 1.7, 12.0), and the interaction between these terms was highly significant in multivariable analysis, suggesting the combined importance of both genetic factors and maternal smoking.

Park and Kim (1986) studied 3,651 children aged 0 to 14 from a randomized, clustered sample of households in South Korea (response rate: 89%). A questionnaire was administered to household members about their smoking habits and respiratory symptoms. Mothers answered questions about the presence of cough in the child in the 3 months prior to interview. The authors reported dose-response relationships between the child's cough and number of smokers in the family, number of smokers in the same room, number of cigarettes smoked by all family members, and number of cigarettes smoked by parents. The relationship was present in children of different ages (less than 5 years, 6 to 11 years, and 12 to 14 years). The authors controlled for parental education, socioeconomic status, birth rank, parental age, birth interval, number of family members, and number of siblings. Family members with cough or with morning phlegm production were significantly more likely to live with children with cough. After correcting for these two factors, chronic cough was 2.4 times as likely in children of families whose members smoked 1 to 14 cigarettes per day (95% C.I. = 1.4, 4.3) and 3.2 times as likely in children of families whose members smoked more than 15 cigarettes per day (95% C.I. = 1.9, 5.5). However, effects were more noticeable and only reached statistical significance in children of families whose adult members did not have chronic cough.

Bisgaard and coworkers (1987) studied 5,953 infants of a total of 8,423 eligible newborns (71%) enrolled in a prospective study. At the age of 1 year, the child's mother was interviewed regarding episodes of wheeze during the previous year and possible risk factors for wheezing. The risk of wheezing was 2.7 times as high (95% C.I. = 1.8, 4.0) in children whose mothers smoked three or more cigarettes per day as in children whose mothers smoked fewer than three cigarettes per day. Results were independent of social status and sex of the child. The authors decided not to control for quarter of birth or use of day-care facilities, with the assumption that these factors did not modify the relationship between maternal smoking and wheezing. Also, biases could have been introduced by the fact that almost one-third of the original sample was not included in the analysis.

Geller-Bernstein and coworkers (1987) studied 80 children aged 6 to 24 months who had been seen as outpatients or inpatients in Israel for wheezing and who had a diagnosis of atopy.

The children were examined every 6 months during 4 years by a physician. At the end of assessment, the authors classified children as having "recovered" if they had been symptom-free for at least 1 (the last) year; otherwise they were classified as "persistent wheezers." "Persistent wheezers" were more likely to have smoking parents than were "recovered" children (OR = 3.1, 95% C.I. = 1.1, 8.9). This result was independent of changes in IgE levels during the study period. The authors did not control for the possible confounding effect of parental symptoms.

Cogswell and coworkers (1987) studied 100 newborns who had at least one parent with a history of hay fever or asthma. Ninety-two children were still being followed at 1 year of age and 73 at the age of 5 years. Children were examined periodically and whenever they had signs of respiratory illness. At the child's first birthday, the number of those who had developed wheezing was equally distributed between parents who did or did not smoke. By the age of 5 years, however, 62% of parents who smoked had children who had wheezed compared with 37% in nonsmoking families ($p < 0.05$). It is unlikely that these results can be explained by the confounding effect of parental symptoms, because all parents were allergic by definition. It is also quite unlikely that preferential withdrawal of nonwheezing children of smoking parents could have biased the results.

Toyoshima and coworkers (1987) from Osaka, Japan, followed 48 of 65 wheezy infants and children less than 3 years old for up to 4 years. Outcome information was obtained from charts or by telephoning the child's mother. Among 18 children who were still symptomatic 25 to 44 months after their first visit, 17 lived with smokers compared with 13 of 22 children who lived with smokers and who stopped having symptoms during followup (OR = 11.8, 95% C.I. = 1.3, 105.0). Results were independent of family history of allergy, feeding practices, and disturbances at birth. Selection bias related to the number of subjects lost for followup or with missing information could have influenced the results of this study.

Tsimoyianis and collaborators (1987) evaluated the effects of exposure to ETS on respiratory symptoms in a group of 12- to 17-year-old high school athletes (N = 193). Histories of smoking by all household members were obtained for all subjects. Athletes exposed to ETS at home were more likely to report cough than were unexposed athletes ($p = 0.08$). Frequency of bronchitis, wheeze, and shortness of breath was similar in both groups. A greater awareness of the smoking habits of those around them by subjects with cough cannot be excluded as an explanation of these findings, but this source of bias cannot explain the exposure-response trends for ETS and lung function seen in this same sample (see Section 7.8.1).

Andrae and collaborators (1988) mailed questionnaires to the parents of 5,301 children aged 6 months to 16 years living in the city of Norrkoping, Sweden. Data were obtained from 4,990 children (94% response rate). Children with parents who smoked had exercise-induced

cough more often than did children of nonsmokers (OR = 1.4, 95% C.I. = 1.1, 1.8). Exposure to ETS interacted with living in houses with damage by dampness; children exposed to both had more exercise-induced cough and allergic asthma when compared to those exposed to only one or neither. Results of this cross-sectional study may have been biased by preferential reporting of symptoms by smoking parents, although a reliability study performed in a random sample was reported to confirm 95% of the answers regarding respiratory symptomatology. In addition, no effort was made to control for active smoking in older children.

Somerville and coworkers (1988) enrolled 88% of 8,118 eligible children aged 5 to 11 from England and Scotland. Data on the child's respiratory symptoms and parental smoking were obtained from a self-administered questionnaire completed by the child's mother. After exclusions for missing data, the proportions of children available ranged from 60.9% to 63.9% of all subjects, depending on the variables involved. Logistic regression analysis was used to control for child's age, presence of siblings, one- or two-parent families, paternal employment, social class, maternal smoking during pregnancy, overcrowding, maternal education, maternal age, triceps skinfold thickness, and birthweight. For Scottish children (who were only 19% of all subjects), the authors found a significant relationship between number of cigarettes smoked at home and "chest ever wheezy" ($p < 0.01$; OR not reported). Among English children, there was a significant relationship between number of cigarettes smoked at home by mother and father together and prevalence of a wheezy or whistling chest most nights (adjusted OR in children whose parents smoked 20 cig./day = 1.6; 95% C.I. = 1.2, 2.2). Attacks of bronchitis and cough during the day or at night were also significantly correlated with number of cigarettes smoked by parents in the English sample; odds ratios in children of parents who smoked 20 cigarettes per day were 1.4 and 1.3, respectively, but no confidence intervals were reported. The authors concluded that the effect of parental smoking on respiratory symptoms in this age group is small and requires a large number of subjects to be detected.

Rylander and collaborators (1988) from Stockholm, Sweden, studied 67 children aged 4 to 7 years who had been hospitalized with virologically proven RSV infections before age 3. Questionnaires were mailed to parents regarding their smoking habits and the child's history of wheezing illnesses after the initial episode. Children who had subsequent occasional wheezing (N = 21) were more likely to have smoking parents than those (N = 24) who had no subsequent respiratory symptoms (OR = 4.3, 95% C.I. = 1.1, 16.4). However, frequency of parental smoking among children who had no subsequent respiratory symptoms was not significantly different from that of children who had subsequent recurrent wheezing. The inconsistency of the results in this study may be explained by the small number of subjects involved.

Strachan (1988) studied 1,012 of a target sample of 1,095 schoolchildren aged 6.5 to 7.5 years in Edinburgh, Scotland. Parents answered a questionnaire on their smoking habits and on respiratory symptoms in their children. There was no relationship between number of smokers in the household and prevalence of wheezing in the population. Cough at night (> 3 nights in the past month) was more likely to occur in children living with one smoker (OR = 1.6; 95% C.I. = 1.1, 2.6) or two smokers (OR = 2.5; 95% C.I. = 1.5, 4.0) than in children living with nonsmokers. Occurrence of "chesty colds" in children was also more frequent in households with one (OR = 1.3; 95% C.I. = 0.9, 1.9) or two smokers (OR = 1.9; 95% C.I. = 1.3, 3.0).

A subsequent report (Strachan et al., 1990) based on the same population sample studied the relationship between salivary cotinine levels and respiratory symptomatology in a subset of 770 children (see also Strachan et al. [1989], Section 7.4.1). The authors found no relationship between cotinine levels and wheezing or frequent night cough. Frequency of chesty colds was significantly correlated with quintals of salivary cotinine ($p < 0.01$). The authors noted that objective markers of recent exposure to ETS may not adequately reflect exposure at some critical period in the past. They also noted that there may be different ways of understanding the concept of "wheezing" and proposed that this could explain the lack of association between this symptom and both questionnaire-based and cotinine-based assessment of exposure to ETS in their sample.

Lewis and coworkers (1989) performed a case-control study of risk factors for chronic cough in children under 6 years in Salford, United Kingdom. They enrolled 60 children referred to a pediatric outpatient clinic with cough lasting more than 2 months or frequent episodes of cough without wheeze. These 60 subjects were compared with controls admitted for routine surgical procedures. Children with chronic cough were 1.7 times (95% C.I. = 0.8, 3.5) as likely to live with a smoker as were controls. Because of the small number of subjects and the high prevalence of parental smoking (> 50%), the power of this study may have been too low to allow for meaningful conclusions.

Neuspiel and coworkers (1989) studied 9,670 of 9,953 eligible children enrolled at birth in Great Britain. Information on parental smoking was obtained at birth, at age 5 years, and at age 10 years. Outcome data were obtained from maternal interviews when the children were 10 years old. Children of smoking mothers had 11% higher risk (95% C.I. = 2%, 21%) of wheezing between ages 1 and 10 than did children of nonsmoking mothers. An exposure-response relationship was also present: Cumulative incidence was 5.2% in children whose mothers were nonsmokers, 6.6% in children whose mothers smoked 1 to 4 cigarettes per day, 7.5% in children whose mothers smoked 5 to 14 cigarettes per day, 8.1% in children whose mothers smoked 15 to 24 cigarettes per day, and 8.9% in children whose mothers smoked more than 24 cigarettes per day. The risk also was increased in children of mothers who did not smoke during pregnancy but were smokers

thereafter (RR = 2.2, 95% C.I. = 1.2, 3.9). The association persisted after a logistic regression model was used to control for the effect of child's sex, child allergy, paternal smoking, parental allergy, crowding, bedroom dampness, feeding practices, gas cooking, and social status. The increase in risk was cut approximately in half but did not disappear when additional corrections for maternal respiratory symptoms and for a measure of maternal depression were made. Results of this study may be explained in part by preferential reporting of wheezy illnesses by smoking mothers. However, it is unlikely that the association between maternal smoking and wheezy illnesses found in this study can be explained exclusively by uncontrolled sources of bias; there was a striking exposure-response effect, and the association persisted after controlling for most known confounders and was independent of maternal smoking during pregnancy.

Chan and collaborators (1989a) studied 134 children aged 7 years out of 216 eligible infants of under 2,000 g birthweight who were admitted to the neonatal unit of two hospitals in London, England. Parents of these 134 children and of 123 control schoolchildren born in the same period but with normal birthweight completed a self-administered questionnaire on respiratory illnesses and on social and family history. At age 7, children whose mothers smoked were at increased risk of having frequent wheeze independent of their neonatal history (adjusted OR = 2.7; 95% C.I. = 1.3, 5.5), although the increase only reached statistical significance for children of normal birthweight. Prevalence of frequent cough was also more likely to occur in children of smoking mothers (OR = 2.4, 95% C.I. = 1.3, 4.6), and the association was significant for both cases and controls studied separately. The authors performed a logistic regression to control for possible confounders (only the low-birthweight group was included). The relationship between frequent wheeze and maternal smoking persisted among low-birthweight children after controlling for family history of asthma, atopy, socioeconomic status, and use of neonatal oxygen. The relationship between frequent cough and maternal smoking was no longer significant among low-birthweight infants after controlling for the same possible confounders. For the low-birthweight group, the authors assessed the reliability of some of the responses to their questionnaires; there was a high correlation (r = 0.96) between the number of hospitalizations reported by parents and those documented in the outpatient clinic of the neonatal unit that followed the infants. The authors concluded that misclassification due to parental failure to recall previous respiratory illnesses in the low-birthweight group was unlikely.

Krzyzanowski and collaborators (1990) studied a sample of 298 children aged 5 to 15 who were family members of county employees enrolled in a prospective study. Parents answered a questionnaire on their smoking habits and on respiratory symptoms in their children. Indoor formaldehyde concentrations in the living environment also were measured. Prevalence rates of chronic bronchitis (as diagnosed by a physician) were significantly higher in children exposed

both to ETS and to formaldehyde concentrations of over 60 parts per billion than in children with one or none of these exposures. The authors also reported that similar effects were not seen in adults.

Dijkstra and collaborators (1990) obtained consent for participation in their study for 1,051 of a total of 1,314 (80%) eligible 6- to 12-year-old schoolchildren from a rural area in The Netherlands. Parents completed a self-administered questionnaire on their smoking habits and on respiratory symptoms in their children. Complete information was available for 775 children. When compared to children of nonsmoking households, children exposed to ETS at home were significantly more likely to have cough on most days for at least 3 months consecutively (OR = 2.5, 95% C.I. = 1.1, 5.6), wheezy or whistling sounds in the chest in the last year (OR = 1.9; 95% C.I. = 1.0, 3.5), and attacks of shortness of breath with wheeze in the last year (OR = 2.0; 95% C.I. = 0.9, 4.2). Exposed children were significantly more likely to have one or more of the above symptoms than were unexposed children (OR = 2.0; 95% C.I. = 1.2, 3.7). Results were still significant after adjusting for parental respiratory symptoms and for maternal smoking during pregnancy. The authors also measured nitrogen dioxide in the homes of all children but found no association of the latter with respiratory symptoms.

Mertsola and coworkers (1991) followed prospectively for 3 months 54 patients aged 1 to 6 years from Turku, Finland, who had a history of recurrent attacks of wheezy bronchitis. The parents were told to record the symptoms of the child daily and were asked to bring their child to the hospital emergency room if the child developed signs of an acute respiratory infection. Incidence of prolonged wheezing episodes (> 4 days) during followup was significantly more likely in children exposed to ETS than in unexposed children (OR = 4.8; 95% C.I. = 1.9, 12.6). The result was independent of number of siblings, age, sex, medication, and personal history of allergy.

7.5.2. Summary and Discussion on Cough, Phlegm, and Wheezing

Recent studies reviewed in this report that were not included either in the Surgeon General's report (U.S. DHHS, 1986) or in the NRC report (1986) substantially confirm the conclusions reached in those two reports. There is sufficient evidence for the conclusion that ETS exposure at home is causally associated with respiratory symptoms such as cough, phlegm, or wheezing in children.

The evidence is particularly strong for infants and preschool children; in this age range, most studies have found a significant association between exposure to ETS (and especially to maternal smoking) and respiratory symptoms in the children, with odds ratios generally ranging between 1.2 and 2.4. Selection bias may have influenced the results of certain cross-sectional

studies; retrospective studies also may have been biased by preferential recall of their children's symptoms by smoking parents. However, the presence of a causal relationship is strongly supported by the consistency of the results for different geographic areas (Japan, Korea, People's Republic of China, Europe, and North America) and by the positive findings in prospective studies that are less subject to selection and recall biases.

In addition, efforts have been made by all researchers to control for possible confounders and to avoid sources of bias. It is not feasible for each study to take into account all possible factors that may affect the relationship under study; some of these factors may even be unknown at present. However, all reviewed studies have controlled for at least some of the best-known confounders (family history of respiratory illnesses, parental respiratory symptoms, socioeconomic status, crowding, presence of other siblings, home dampness, gas cooking, maternal level of education, perinatal problems, low birthweight, maternal age, birth rank, and maternal stress, or depression). Of these possible confounders, a history of respiratory symptoms in parents has been particularly scrutinized. The NRC report (1986) noted that bias may be introduced by parents who have a history of respiratory illnesses for several reasons. These parents may overstate their children's symptoms, or their children actually may have more respiratory illnesses and symptoms. The latter possibility could be the result of intrafamily correlation of susceptibility (referred to as familial resemblance by Kauffmann and coworkers [1989a]). Because smokers are more likely to have respiratory symptoms, one would expect that controlling for respiratory symptoms in parents would result in a decrease in statistical significance of the relationship between ETS and symptoms in the child. In fact, most recent studies that have addressed the issue report that controlling for family history of respiratory symptoms decreases but does not entirely explain the increased risk of respiratory symptoms in young children exposed to ETS. It has been stressed, however, that the use of these statistical adjustment procedures may induce an underestimation of the effect of passive smoking; this would indeed be the case if parents with symptoms (and thus more likely to be smokers) were more prone to report symptoms in their children than were parents without symptoms. Several studies also have found that the effect is independent of maternal smoking during pregnancy and cannot be attributed exclusively to intrauterine exposure to tobacco products (although the latter may potentiate the effects of postnatal exposure to ETS).

The evidence is significant but less compelling for a relationship between exposure to ETS and respiratory symptoms in school-age children. Odds ratios for this age group are usually between 1.1 and 2.0. Several studies have shown that, among school-age children, there are significant differences in susceptibility to ETS exposure between individuals. There is, in fact, evidence showing that several factors may amplify the effects of passive smoking: prematurity, a family history of allergy, a personal history of respiratory illnesses in early childhood, and being

exposed to other environmental pollutants such as formaldehyde. In addition, long-term exposure may have more important effects than short-term exposure. One study of 7-year-old children (Strachan, 1988; Strachan et al., 1990) used both questionnaires regarding smoking habits in the household and the child's saliva cotinine levels as indices of exposure to ETS. The authors found a significant increase in the risk of having frequent cough when the questionnaire was used to ascertain exposure, but no association between saliva cotinine levels and frequency of cough. As the authors remarked, biochemical markers permit characterization of recent tobacco smoke exposures, but they may not adequately reflect exposure at some critical period in the past. Recent studies of intraindividual variability of cotinine levels also have suggested that it may be misleading to assess the validity of questionnaire measures against a single determination of a biologic marker (Coultas, 1990b; Idle, 1990). It is thus possible that associations evaluated with salivary cotinine are likely to underestimate the true relationship between passive smoking and respiratory morbidity (Strachan et al., 1990).

In the case of older children who may have started experimenting with cigarettes, the confounding effects of active smoking need to be considered. Most researchers have been aware of this problem and have attempted to control for it. A great difficulty lies in misclassification of smokers due to underreporting. Young persons may be reluctant to admit smoking cigarettes. Data are often obtained from parents, who may not be aware of the child's smoking.

In summary, this report concludes that ETS exposure at home causes increased prevalence of respiratory symptoms in infants and young children. There is also good evidence indicating that passive smoking causes respiratory symptoms in some older children, particularly in children who have predisposing factors that make them more susceptible to the effects of ETS.

7.6. EFFECT OF PASSIVE SMOKING ON ASTHMA

Studies addressing the effects of passive smoking on frequency of asthma were directly reviewed only in the Surgeon General's report (U.S. DHHS, 1986) and not explicitly in the report on environmental tobacco smoke by the NRC (1986). The Surgeon General's report concluded that epidemiologic studies of children had shown no consistent relationship between the report of a doctor's diagnosis of asthma and exposure to involuntary smoking. The report pointed out that, although one study had shown an association between involuntary smoking and asthma (Gortmaker et al., 1982), others had not (Schenker et al., 1983; Horwood et al., 1985). This variability was attributed to differing ages of the children studied, differing exposures, or uncontrolled bias. The report also concluded that maternal cigarette smoking may influence the severity of asthma. Alteration of nonspecific bronchial responsiveness was proposed as a mechanism for this latter effect.

7.6.1. Recent Studies on the Effect of Passive Smoking on Asthma in Children

Several new cross-sectional and longitudinal studies published after the U.S. Surgeon General's report (U.S. DHHS, 1986) was released have addressed the relationship between frequency, incidence, and severity of asthma and parental cigarette smoke (Table 7-7). (Studies on the relationship between ETS exposure and bronchial responsiveness were reviewed in Section 7.2.4.)

Burchfield and coworkers (1986) studied 3,482 nonsmoking children and adolescents ages 0 to 19 years out of 4,378 eligible subjects from Tecumseh, Michigan. Subjects or their parents (for children aged 15 years or younger) answered questionnaires on past history of asthma and other respiratory conditions. Information on parental smoking habits was obtained from each parent. Prevalence rates of asthma were higher among children whose parents both had smoked during the child's lifetime than among children whose parents had never smoked. The effect was stronger and only reached statistical significance for males (OR for boys = 1.7, 95% C.I. = 1.2, 2.5 in boys; OR for girls = 1.2, 95% C.I. = 0.8, 1.9). Children with one parental smoker were not more likely to have asthma than was the unexposed reference group. When results were stratified by parental history of respiratory conditions, there was some reduction in the magnitude of the parental smoking effects, but results remained significant for asthma in males. Results were also independent of age, parental education, family size, a diagnosis of hay fever, and a history of other allergies. Reporting bias and diagnostic bias may in part explain the relationships reported in this study; smoking parents may be more likely to report asthma in their children, and physicians may be more prone to diagnose asthma in children of smoking parents.

D. Evans and coworkers (1987) studied 191 out of 276 children aged 4 to 17 years from low- income families who were receiving health care for physician-diagnosed asthma in New York. Excluded children were younger and had fewer emergency room visits for asthma than those with complete data. The authors suggested that the latter subjects had more severe asthma than the general community population of low-income children with asthma. Emergency room visits and hospitalizations for asthma were assessed by reviewing hospital records. Passive smoking by the child was measured by asking one parent if he or she or anyone else in the house smoked. Authors did not differentiate between maternal and paternal smoking; no attempt was made to assess the degree of exposure to cigarette smoke. Eight children who were active smokers were excluded. There was a significant correlation between number of emergency room visits and cigarette smoke exposure ($p = 0.008$); the mean frequency ($\pm$ SD) of annual emergency room visits observed for children exposed to passive smoking was 3.1 ± 0.4, compared with 1.8 ± 0.3 for children from nonsmoking households. Passive smoking had no effect on either the frequency of days with asthma symptoms or on the annual frequency of hospitalizations. Results were

Table 7-7. Recent epidemiologic studies of effects of passive smoking on asthma in childhood

Authors	Population studied	ETS exposure assessment	Outcome variable	Results[1]	Observations
Burchfield et al. (1986)	3,482 nonsmoking children 0 to 19 yr. in Tecumseh, Michigan	Questionnaire answered by subjects or parents	Prevalence of asthma	OR = 1.7 (1.2, 2.5) for boys; OR = 1.2 (0.8, 1.9) for girls	Independent of parental respiratory illness, age, parental education, family size, and allergies
D. Evans et al. (1987)	191 children aged 4 to 17 yr. in New York, New York	Parental questionnaire	Emergency room visits and hospitalizations for asthma (from medical records)	3.1 ± 0.4 vs. 1.8 ± 0.3 (p=0.008) emergency room visits in children of smoking and non-smoking parents	No distinction made between maternal and paternal smoking; independent of race and parental employment status
O'Connor et al. (1987)	292 subjects aged 6 to 21 yr. in Boston, Massachusetts	Parental questionnaire	Bronchial response to cold air	Significantly increased response in asthmatics whose mothers smoked	No increase in nonasthmatics whose mothers smoked

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Table 7-7. (continued)

Authors	Population studied	ETS exposure assessment	Outcome variable	Results[1]	Observations
Murray and Morrison (1989)	415 children aged 1 to 17 yr. with asthma in Vancouver, Canada	Parental questionnaire	Asthma symptom score for severity of asthma	Higher scores ($p<0.01$) in children of smoking mothers	Stronger effect in boys and older children
Krzyzanowski et al. (1990)	298 children aged 5 to 15 yr. in Tucson, Arizona	Parental questionnaire	Parental reports of asthma in their children	OR = 9.0 (2.4, 34.0) for children exposed to ETS and formaldehyde vs. nonexposed	Small sample
Sherman et al. (1990)	770 children aged 5 to 9 yr. followed for 11 yr. in Boston, Massachusetts	Parental and subject questionnaire	Physician diagnosis of asthma	No effect of parental smoking on prevalence or incidence of asthma	No effort to assess effect of heavy smoking by parents; no control for socioeconomic status
Weitzman et al. (1990)	4,331 children aged 0 to 5 yr. (U.S. National Health Interview Survey)	Maternal questionnaire	Asthma for at least 3 mo. at time of questionnaire	OR = 2.1 (1.3, 3.3) for children whose mothers smoked ≥10 cig./day	Independent of race, sex, family size, presence of both parents, and number of rooms

(continued on the following page)

Table 7-7. (continued)

Authors	Population studied	ETS exposure assessment	Outcome variable	Results[1]	Observations
Oldigs et al. (1991)	11 asthmatic children	Direct exposure to ETS for 1 hour	Changes in lung function	No effect	No assessment of effect of chronic exposure
Martinez et al. (1992)	774 children aged 0 to 5 yr. followed for several years in Tucson, Arizona	Parental questionnaire	Physician diagnosis of asthma	OR = 2.5 (1.4, 4.6) for children of low maternal education whose mothers smoked ≥10 cig./day	No effect among children of better educated mothers
Ehrlich et al. (1992)	228 children; 72 with acute asthma; 35 with nonacute asthma and 121 controls	Cotinine levels in urine of children; smoking by maternal caregiver	Emergency room and asthma clinic visits	Higher levels of cotinine in asthmatics OR = 1.9 (1.0, 3.4)	Similar cotinine levels in acute and nonacute asthmatics

[1]95% confidence intervals in parentheses.

independent of ethnicity and parental employment status. The association could have been explained by lower compliance with prescribed treatment of their children's asthma by smoking parents, but the authors found no significant differences in compliance (as assessed by an index of asthma self-management activities) between smoking and nonsmoking parents. The authors estimated that the additional cost for emergency care for asthma was $92 ± $68 per family per year.

O'Connor and coworkers (1987) performed bronchial challenges with subfreezing air in 292 subjects 6 to 21 years of age. They were selected from 879 eligible subjects of the same age who were participating in a longitudinal study on respiratory illnesses in East Boston. An attempt was made to include as many subjects as possible who reported a history of asthma or wheezing on standardized questionnaires. Therefore, the latter group of subjects were overrepresented among those tested. The change in FEV_1 caused by subfreezing air was significantly higher in asthmatic subjects whose mothers smoked at least one cigarette per day than in those whose mothers were nonsmokers. This relationship was independent of age, sex, height, personal smoking, paternal smoking, atopy, and baseline lung function. There was no relationship between maternal smoking and response to cold air among nonasthmatics.

Murray and Morrison (1989) studied 415 nonsmoking children aged 1 to 17 years consecutively referred to an allergy clinic in Vancouver, Canada, for asthma or recurrent wheezing of the chest. Questionnaires were administered to the parents of all children at the time of their first visit. Forced expiratory flows and bronchial reactivity to histamine also were measured. An asthma symptom score was calculated for each subject based on the severity of asthma and the need for medication, as reported by parents. Children of smoking mothers had significantly higher indices of asthma severity ($p < 0.01$) and significantly lower FEV_1 (84.4% predicted vs. 77.3% predicted, $p < 0.01$) than did children of nonsmoking mothers. They were also significantly more responsive to histamine than were children of nonsmoking mothers ($p = 0.01$). The effect was present in both genders but was stronger for boys than for girls. Also, the effect was stronger for older children (12 to 17 years of age) than for children 6 years of age or younger. The authors also reported a positive correlation between length of exposure to ETS and asthma symptom score. It is unlikely that these results can be explained by parental overreporting because the association between passive smoking and severity of symptoms paralleled that between passive smoking and objective measurements of severity.

In their previously reviewed report (Section 7.5.1), Krzyzanowski and coworkers (1990) found that children exposed to ETS and to more than 60 ppb of formaldehyde had significantly higher prevalence rates of asthma than those exposed to only one of these contaminants or to none (OR for the latter comparison = 9.0; 95% C.I. = 2.4, 34.0). No such association was seen among

adult household members. It is unlikely that this association is attributable to parental overreporting of asthma because the authors relied on objective measurement of indoor formaldehyde concentrations.

Sherman and collaborators (1990) reported on the results of a longitudinal study of determinants of asthma in a sample of 770 schoolchildren enrolled in East Boston in 1974. Questionnaires were used to obtain data on respiratory symptoms and illnesses, cigarette smoking history of parents and children, and household demographics. They were administered on entry and for 11 consecutive years (1978-1988). Parents answered for children aged 9 or less, except for questions on the child's smoking history. The authors identified risk factors for the onset of asthma, the occurrence of which antedated the time of first diagnosis of asthma. There was no significant relationship between maternal smoking and either prevalence of asthma at the first survey or incidence of new cases of asthma during followup (sex-adjusted RR = 1.1; 95% C.I. = 0.7, 1.7). The authors considered it unlikely that this finding could be due to exposure levels too low to increase the risk of asthma. However, no effort was made to assess the relationship between incidence of asthma and number of cigarettes smoked by parents. Likewise, no effort was made to determine the possible role of factors known to modify exposure to ETS such as parental socioeconomic level (Strachan et al., 1989).

Weitzman and coworkers (1990) studied 4,331 children aged 0 to 5 years who were part of the U.S. National Health Interview Survey. Children were categorized as having asthma if their parents reported that asthma was current at the time of interview and had been present for more than 3 months. Mothers were asked about their smoking habits during and after pregnancy. Odds of having asthma were 2.1 times as high (95% C.I. = 1.3, 3.3) among children of mothers who smoked 10 or more cigarettes per day than among children of nonsmoking mothers. The risk of having asthma was not significantly increased in children of mothers who smoked fewer than 10 cigarettes per day. Use of asthma medication was also more frequent among children of mothers who smoked 10 or more cigarettes per day (OR = 4.1; 95% C.I. = 1.9, 8.9). Results did not change significantly after controlling for gender, race, presence of both parents, family size, and number of rooms in the households. No information was available on parental respiratory symptoms or socioeconomic status. The results of this study could be explained partially by overreporting of asthma by smoking mothers.

Oldigs and collaborators (1991) exposed 11 asthmatic children to ETS and to ambient air for 1 hour. They found no significant difference in lung function or in bronchial responsiveness to histamine after ETS exposure when compared with sham exposure. The study was designed only to determine if acute exposures to ETS caused immediate effects, and it did not assess the changes induced by chronic exposure to ETS.

Martinez and coworkers (1992) studied incidence of new cases of asthma in a population sample of 774 out of 786 eligible children aged 0 to 5 years enrolled in the Tucson study of chronic obstructive lung disease. At the time of enrollment, the child's parents answered standardized questionnaires about personal respiratory history and cigarette smoking habits. Surveys were performed on an approximately yearly basis, and parents were asked if the child had been seen by a doctor for asthma in the previous year. There were 89 (11.5% of the total) new cases of asthma during followup. Children of mothers with 12 or fewer years of formal education and who smoked 10 or more cigarettes per day were 2.5 times as likely (95% C.I. = 1.4, 4.6) to develop asthma as were children of mothers with the same education level who did not smoke or who smoked fewer than 10 cigarettes per day. This relationship was independent of self-reported symptoms in parents. Decrements in lung function paralleled the increase in asthma incidence. No relationship was observed between maternal smoking and asthma incidence among children of mothers with more than 12 years of formal education.

Ehrlich et al. (1992) studied 72 children with acute asthma recruited in the emergency room; 35 nonacute asthmatic children from an asthma clinic; and 121 control children without asthma from the emergency room. They assessed exposure to ETS both by questionnaire and by measurement of urinary levels of cotinine/creatinine ratios. Smoking by maternal caregiver was significantly more prevalent among asthmatic children (OR = 2.0, 95% C.I. = 1.1, 3.4). This was confirmed by a significant difference between groups in prevalence of cotinine to creatinine ratio of greater or equal to 30 ng/mg (OR = 1.9; 95% C.I. = 1.0, 3.4). There was no difference in exposure indices between acute and nonacute asthmatics. The authors concluded that smoking by a maternal caregiver was a significant risk factor for clinically significant asthma in children.

7.6.2. Summary and Discussion on Asthma

There is now sufficient evidence to conclude that passive smoking is causally associated with additional episodes and increased severity of asthma in children who already have the disease. Several studies have found that bronchial responsiveness is more prevalent and more intense among asthmatic children exposed to maternal smoke. Emergency room visits are more frequent in children of smoking mothers, and these children also have been found to need more medication for their asthma than do children of nonsmoking mothers (see Table 7-4).

A simple bronchospastic effect of cigarette smoke is probably not responsible for the increased severity of symptoms associated with passive smoking because acute exposure to ETS has been found to have little immediate effect on lung function parameters and airway responsiveness in asthmatic children. Therefore, the mechanisms by which passive smoking enhances asthma in children who already have the disease are likely to be similar to those

responsible for inducing asthma and entail chronic exposure to relatively high doses of ETS (see discussion below). Murray and Morrison (1988) reported that ETS exposure decreased lung function and increased medication requirements in asthmatic children only during the cold, wet season and not during the dry, hot season in Vancouver, Canada. These seasonal differences may be at least partly explained by the finding by Chilmonczyk and collaborators (1990) that urine cotinine levels of children exposed to ETS are significantly higher in winter than in summer. These seasonal fluctuations also suggest that the effects of passive smoking on asthma severity are reversible and that decreasing exposure to ETS could prevent many asthmatic attacks in affected children.

New evidence available since the Surgeon General's report (U.S. DHHS, 1986) and the NRC report (1986) also indicates that passive smoke exposure increases the number of new cases of asthma among children who have not had previous episodes (see Table 7-7 for results and references). Although most studies are based on parental reports of asthma, it is highly unlikely that the relationship between asthma and ETS exposure is entirely attributable to reporting bias. In fact, concordance in the relationship between ETS exposure and both questionnaires and objective parameters such as lung function or bronchial provocation tests has been reported in several studies. The association is also biologically plausible; the mechanisms that are likely to be involved in the relationship between ETS exposure and asthma have been discussed extensively in Section 7.2. The consistency of all the evidence leads to the conclusion that ETS is a risk factor for inducing new cases of asthma. The evidence is suggestive of a causal association but is not conclusive.

Data suggest that levels of exposure required to induce asthma in children are high; in fact, most recent and earlier studies that classified children as exposed to ETS if the mother smoked one cigarette or more usually failed to find any effect of ETS on asthma prevalence or incidence. Furthermore, two recent large studies found an increase in the prevalence (Weitzman et al., 1990) or incidence (Martinez et al., 1992) of asthma only if the mother smoked 10 cigarettes or more per day. It is also important to consider that, for any level of parental smoking, exposure to ETS is higher in children belonging to families of a lower socioeconomic level (Strachan et al., 1989) and that the relationship of maternal smoking to asthma incidence may be stronger in such families (Martinez et al., 1992). Concomitant exposure to other pollutants also may enhance the effects of ETS (Krzyzanowski et al., 1990).

7.7. ETS EXPOSURE AND SUDDEN INFANT DEATH SYNDROME

The relationship between ETS exposure and sudden infant death syndrome (SIDS) was not addressed in either the Surgeon General's report (U.S. DHHS, 1986) or in the NRC report (1986).

Because of the importance of this syndrome as a determinant of infant mortality and because of the available evidence of an increased risk of SIDS in children of smoking mothers, the issue has been added to this report (Table 7-8).

SIDS is the most frequent cause of death in infants aged 1 month to 1 year. Approximately 2 of every 1,000 live-born infants (more than 5,000 in the United States alone each year) die suddenly and unexpectedly, usually during sleep, and without significant evidence of fatal illness at autopsy (CDC, 1989b). The cause or causes of these deaths are unknown. The most widely accepted hypotheses suggest that some form of respiratory failure is involved with most cases of SIDS.

In 1966, Steele and Langworth (1966) first reported that maternal smoking was associated with an increased incidence of SIDS. They studied the hospital records of 80 infants who had died of SIDS in Ontario, Canada, during 1960-1961 and compared them with 157 controls matched for date of birth, sex, hospital at which the child was born, and parity of the mother. Infants of mothers who smoked 1 to 19 cigarettes per day were twice as likely (OR = 2.1; 95% C.I. = 1.1, 3.8) to die of SIDS as were infants of nonsmoking mothers. The odds ratio was 3.6 (95% C.I. = 1.7, 7.9) when infants of mothers who smoked 20 or more cigarettes per day were compared to infants of nonsmoking mothers. The authors reported that the risk of dying of SIDS was higher in low-birthweight infants whose mothers smoked when compared with low-birthweight infants whose mothers did not smoke. However, they made no effort to control for other confounders that were related both to maternal smoking and to SIDS, such as maternal age and socioeconomic status. In addition, they made no reference to the relative roles of in utero exposure to tobacco smoke products and postnatal ETS exposure.

Naeye and collaborators (1976) studied 59,379 infants born between 1959 and 1966 in participating hospitals from several U.S. cities. After meticulous investigation of clinical and postmortem material, they identified 125 of these infants (2.3 per 1,000 live births) as having died of SIDS and compared them with 375 infants matched for place of birth, date of delivery, gestational age, sex, race, and socioeconomic status. Infants of mothers who smoked were more than 50% more likely (OR = 1.6; 95% C.I. = 1.0, 2.4) to die of SIDS than were those of mothers who denied smoking. When compared with the latter, infants of mothers who smoked six or more cigarettes per day were 2.6 times more likely (95% C.I. = 1.7, 4.0) to die of SIDS. The authors made no attempt to distinguish between in utero exposure to tobacco smoke products and ETS exposure after birth.

Bergman and Wiesner (1976) selected 100 well-defined cases of SIDS occurring in white children in King County, Washington. These cases were matched for race, sex, and birth date with 100 controls. Questionnaires were mailed to the mothers of cases and controls, but only 56

Table 7-8. Epidemiologic studies of effects of passive smoking on incidence of sudden infant death syndrome (SIDS)

Authors	Population studied	ETS exposure assessment	Results[1]	Observations
Steele and Langworth (1966)	80 infants who died of SIDS; 157 matched controls in Ontario, Canada	Maternal report from hospital record at birth	OR = 2.1 (1.1, 3.8) when mother smoked 1 to 19 cig./day; OR = 3.6 (1.7, 7.9) when mother smoked ≥20 cig./day	No control for socio-economic status or maternal age
Naeye et al. (1976)	59,379 infants born in several U.S. cities	Maternal report from hospital record at birth	OR = 1.6 (1.0, 2.4) for any maternal smoking; OR = 2.6 (1.7, 4.0) for mothers smoking ≥6 cig./day	Controlling for place of birth, date of delivery, gestational age, sex, race, and socioeconomic status
Bergman and Wiesner (1976)	100 cases of SIDS; 100 matched controls in King County, Washington	Maternal question-naire answered after death (or at equivalent age for controls)	OR = 2.4 (1.2, 4.8); effect only significant for mothers ≤25 yr. (OR = 4.4 [1.7, 11.2])	Independent of maternal education, race, sex, and birth date
Lewak et al. (1979)	44 cases of SIDS	Maternal questionnaire	OR = 4.4 (2.1, 9.2)	No control for possible confounding factors
Malloy et al. (1988)	305,000 births in Missouri	Maternal reports on birth certificate	OR = 1.8 (1.4, 2.2)	Controlling for marital status, maternal age, education, parity, and birthweight

(continued on the following page)

Table 7-8. (continued)

Authors	Population studied	ETS exposure assessment	Results[1]	Observations
Hoffman et al. (1988)	800 SIDS cases; 1,600 controls (NICHD cooperative study)	Maternal questionnaire	OR = 3.4 ($p<0.005$)	Controlling for age, birthweight, and race
Haglund and Cnattingius (1990)	279,000 births in Sweden	Maternal questionnaire	OR = 1.8 (1.2, 2.6). Heavy-smoking mother: OR = 2.7 (1.9, 3.9)	Independent of birthweight, maternal age, social status, parity, sex, and type of birth
Mitchell et al. (1991)	162 SIDS cases; 3 to 4 times as many controls	Parental questionnaire	Cig./day: 1 to 9 — OR: 1.9 (1.0, 3.5); 10 to 19 — 2.6 (1.5, 4.7); ≥20 — 5.1 (2.9, 9.0)	Independent of prenatal care, maternal age, education, marital status, sex, neonatal problems, parity, birthweight, race, season of death, and breastfeeding

[1]95% confidence intervals in parentheses.

cases and 86 controls returned them. Mothers who did not respond tended to be younger and poorer. A higher proportion of mothers of SIDS victims smoked cigarettes during pregnancy (61% vs. 42%). Infants of mothers who smoked after delivery were 2.4 times as likely (95% C.I. = 1.2, 4.8) to die of SIDS as were infants of nonsmoking mothers. The relationship between postnatal exposure to ETS and SIDS was significantly stronger and only reached statistical significance for mothers aged 25 years or less (OR = 4.4; 95% C.I. = 1.7, 11.2). Infants of mothers aged 25 years or less who smoked 20 or more cigarettes per day were 7.7 times as likely to die of SIDS (95% C.I. = 1.7, 35.4) as were infants of nonsmoking mothers. Effects were independent of maternal education. The authors did not try to determine the independent effects of prenatal and postnatal exposures to maternal smoking on the incidence of SIDS.

Lewak and coworkers (1979) studied all infants who died during the first year of life and who were enrolled in a health plan in Oakland, California. Using predefined criteria, they classified 44 infants (2.3 per 1,000 live births) as having died of SIDS and compared them with the rest of the population for several possible risk factors for SIDS. Mothers of infants who died of SIDS were 4.4 times (95% C.I. = 2.1, 9.2) as likely to be smokers as mothers of infants who survived. Paternal smoking had no significant influence on SIDS frequency. The authors made no effort to control for possible confounding factors, nor did they discriminate between the possible roles of prenatal and postnatal exposure to tobacco smoke products.

Malloy and coworkers (1988) linked birth and death certificates to study possible risk factors for neonatal and postneonatal mortality in over 305,000 singleton white live births in Missouri. They identified 372 infants whose deaths were attributed to SIDS (1.2 per 1,000 live births). Infants whose mothers smoked were 1.8 times as likely (95% C.I. = 1.4, 2.2) to die of SIDS than were infants of nonsmoking mothers. This relationship was independent of maternal marital status, education level, age, parity, and child's birthweight. There were no data available that would have allowed one to differentiate the effects of prenatal and postnatal exposure to tobacco smoke products.

Hoffman and collaborators (1988) reported on the results of the National Institute of Child Health and Human Development Cooperative Epidemiological Study of Sudden Infant Death Syndrome risk factors. They studied 800 SIDS cases and 1,600 control infants collected at six study centers across the United States. Control infants were matched for age only (N = 800) or for age, low birthweight, and race (N = 800). SIDS cases were 3.8 and 3.4 times as likely to have smoking mothers as the first and second control groups mentioned earlier, respectively ($p < 0.005$ for both comparisons). There were no data on prenatal and postnatal exposure to tobacco smoke products.

Haglund and Cnattingius (1990) examined risk factors for SIDS in a prospective study based on more than 279,000 Swedish infants who survived the first week of life. SIDS was reported as the sole cause of death in 190 infants (0.7 per 1,000), and in most cases the diagnosis was confirmed by the results of an autopsy. Infants of mothers who smoked one to nine cigarettes per day were 1.8 times as likely (95% C.I. = 1.2, 2.6) to die of SIDS as were infants of nonsmoking mothers. Infants of mothers who were heavy smokers had an even higher risk (OR = 2.7; 95% C.I. = 1.9, 3.9) of dying of SIDS, suggesting an exposure-response relationship. These findings were independent of birthweight, maternal age, social situation, parity, sex, and type of birth. No information was available regarding smoking in the household by either mother or father after the infant's birth.

Mitchell and coworkers (1991) studied SIDS cases occurring in several health districts in New Zealand between November 1, 1987, and October 31, 1988. After careful assessment of the material available from necropsy, 162 infants were classified as having died of SIDS (3.6 per 1,000 live births). These cases were matched for age with three to four times as many controls. The researchers interviewed the parents and obtained complete information for 128 cases and 503 controls. Information on maternal smoking during pregnancy (as a yes/no variable) was obtained from the obstetric records, whereas information on number of cigarettes smoked by the mother in the 2 weeks preceding the interview was obtained from questionnaires. Mothers of infants who died of SIDS were 3.3 times as likely (95% C.I. = 2.2, 5.0) to smoke during pregnancy as were mothers of controls. The analysis of the relationship between maternal smoking after the child's birth and frequency of SIDS showed clear evidence of a biological gradient of risk. Odds ratios were as follows: 1.9 (95% C.I. = 1.0, 3.5) for mothers who smoked 1 to 9 cigarettes per day; 2.6 (95% C.I. = 1.5, 4.7) for mothers who smoked 10 to 19 cigarettes per day; and 5.1 (95% C.I. = 2.9, 9.0) for mothers who smoked 20 or more cigarettes per day. The association between maternal smoking and SIDS frequency was independent of antenatal care, maternal age, maternal education, marital status, sex, neonatal problems, parity, socioeconomic status, birthweight, gestational age, race, season of death, sleep position at death, and breastfeeding.

In summary, there is strong evidence that infants whose mothers smoke are at increased risk of dying suddenly and unexpectedly during the first year of life. This relationship is independent of all other known risk factors for SIDS, including low birthweight and low gestational age. The finding that there is a biological gradient of risk extending from nonsmoking mothers to those smoking more than 20 cigarettes per day adds to the evidence that exposure to cigarette smoke products is involved in the sequence of events that result in SIDS. Available studies cannot differentiate the possible effects with respect to SIDS of exposure to tobacco smoke products in utero from those related to passive smoking after birth. As explained earlier (Section

7.2.2), both human and animal studies show that maternal smoking during pregnancy may modify and potentiate the effects of postnatal ETS exposure. The relationship between maternal smoking and SIDS is independent of low birthweight, which is the most important known effect of maternal smoking during pregnancy. In addition, the incidence of SIDS is apparently associated with days of higher air pollution levels (Hoppenbrouwers et al., 1981), which could indicate a direct effect of airborne contaminants.

In view of the fact that the cause of SIDS is still unknown, it is not possible to assess the biological plausibility of the increased incidence of SIDS related to ETS exposure. Consequently, at this time this report is unable to assert whether or not passive smoking is a risk factor for SIDS.

7.8. PASSIVE SMOKING AND LUNG FUNCTION IN CHILDREN

The Surgeon General's report (U.S. DHHS, 1986) reviewed 18 cross-sectional and longitudinal studies on the effects of ETS exposure on lung function in children (Table 7-9). The report concluded that "the available data demonstrate that maternal smoking reduces lung function in young children" (page 54). The hypothesis was proposed that passive smoking during childhood, by affecting the maximal level of lung function attainable during early adult life, may increase the subsequent rate of decline of lung function and, thus, increase the risk of chronic obstructive lung disease.

The NRC report (1986) reached similar conclusions after reviewing 12 articles (Table 7-9). The authors' summary asserted that "estimates of the magnitude of the effect of parental smoking on FEV_1 function in children range from 0 to 0.5% decrease per year. This small effect is unlikely by itself to be clinically significant. However, it may reflect pathophysiologic effects of exposure to ETS in the lungs of the growing child and, as such, may be a factor in the development of chronic airflow obstruction in later life" (page 215).

7.8.1. Recent Studies on Passive Smoking and Lung Function in Children

Studies appearing since the 1986 reports are presented in Table 7-10.

Lung function measurements were included in the cross-sectional study by O'Connor and collaborators (1987) described earlier (Section 7.6.1). When compared to 97 nonasthmatic children of nonsmoking mothers (mean age $\pm$ SEM = 12.8 $\pm$ 0.3 years), 168 nonasthmatic children of smoking mothers (mean age $\pm$ SEM = 12.9 $\pm$ 0.2 years) had significantly lower mean percentage of predicted FEV_1 (mean $\pm$ SEM = 108.0 $\pm$ 1.4 vs. 101.4 $\pm$ 1.1, respectively, $p < 0.001$) and significantly lower FEF_{25-75} (103.0 $\pm$ 2.3 vs. 88.2 $\pm$ 1.5, respectively, $p < 0.001$). These effects were independent of personal smoking by the child.

Table 7-9. Studies on pulmonary function referenced in the Surgeon General's and National Research Council's reports of 1986

Study	No. of subjects	Age of subjects	Surgeon General	NRC
Berkey et al. (1986)	7,834	Children (6 to 10)	X	X
Brunekreef et al. (1985)	173	Adult women	X	
Burchfield et al. (1986)	3,482	Infants/children (0 to 10)	X	
Chen and Li (1986)	571	Children/adol. (8 to 16)	X	X
Comstock et al. (1981)	1,724	Adults	X	
Dodge (1982)	558	Children (8 to 10)	X	X
Ekwo et al. (1983)	1,355	Children (6 to 12)	X	
Ferris et al. (1985)	10,000	Children/adol. (6 to 13)		X
Hasselblad et al. (1981)	16,689	Children (5 to 17)	X	X
Kauffmann et al. (1983)	7,818	Adults	X	
Kentner et al. (1984)	1,851	Adults	X	
Lebowitz (1984)	117	Families	X	
Lebowitz and Burrows (1976)	271	Children/adol. (<16)	X	X
Schilling et al. (1977)	816	Children/adol. (<18)	X	X
Tager et al. (1979)	444	Children (5 to 19)		X
Tager et al. (1983)	1,156	Children (5 to 9)	X	X
Tashkin et al. (1984)	1,080	Children (7 to 17)	X	X
Vedal et al. (1984)	4,000	Children (6 to 13)	X	
Ware et al. (1984)	10,106	Children (6 to 13)		X
Weiss et al. (1980)	650	Children (5 to 9)	X	X
White and Froeb (1980)	2,100	Adults	X	

Table 7-10. Recent epidemiologic studies on the effects of passive smoking on lung function in children

Authors	Population studied	ETS exposure assessment	Results[1]	Observations
O'Connor et al. (1987)	97 children (12.8 ± 0.3 yr.) of smoking mothers; 168 children (12.9 ± 0.2 yr.) of nonsmoking mothers in Boston, Massachusetts	Parental questionnaire	Nonsmoking mothers vs. smoking mothers: FEV_1 (% predicted) 108.0 ± 1.4 vs. 101.4 ± 1.1 ($p<0.001$); FEF_{25-75} (% predicted) 103.0 ± 2.3 vs. 88.2 ± 1.5 ($p<0.001$)	Independent of personal smoking habits
Lebowitz et al. (1987)	353 subjects aged 5.5 to 25 yr. in Tucson, Arizona	Parental questionnaire	Smoking mothers vs. nonsmoking mothers FVC (residuals) +3.3 vs. -1.4 ($p<0.001$)	Interaction between family history of respiratory illnesses and passive smoking for $V_{max}50\%$ residuals
Tsimoyianis et al. (1987)	132 athletes exposed to ETS; 61 athletes not exposed to ETS	Self-reported exposure to ETS	OR of having low FEF_{25-75} 4.7 (1.1-20.8)	
Kauffmann et al. (1989b)	1,160 French children	Parental questionnaire	Loss of 10 mL of FEV_1, ($p=0.05$); loss of 15 mL/sec of FEF_{25-75} ($p<0.01$)	Independent of sex, town of origin, age, height, weight, and family aggregation of lung function
Chan et al. (1989b)	130 children of low birthweight at age 7 yr. in England	Maternal reports of cigarette smoking	Mean $V_{max}75\%$ (% predicted) in exposed vs. nonexposed 80.7 vs. 91.4 ($p<0.01$)	Independent of sex, birthweight, neonatal respiratory illness, and treatment

(continued on the following page)

Table 7-10. (continued)

Authors	Population studied	ETS exposure assessment	Results[1]	Observations
Dijkstra et al. (1990)	634 children aged 6 to 12 yr. in The Netherlands	Parental questionnaire	Decrease in: FEV_1 (-1.8% [-0.2 to -3.31]); $FEF_{25-75\%}$ (-5.21% [-1.4 to -8.8]); PF (-2.8% [0.6 to -4.8])	Independent of maternal smoking during pregnancy
Strachan et al. (1990)	757 children in Scotland	Salivary cotinine levels	Negative correlation with $FEF_{25-75\%}$ ($p<0.05$) and $V_{max}75\%$ ($p<0.05$)	Approx. 7% difference between maximal exposure and no exposure
Martinez et al. (1992)	774 children enrolled at age 0 to 5 in Tucson, Arizona, and followed for several years	Parental questionnaire	15% lower levels of % predicted $FEF_{25-75\%}$ among children of mothers who smoked and had a low level of education	

[1]95% confidence intervals in parentheses.

Lebowitz and coworkers (1987) reported on the results of a longitudinal study of pulmonary function development in Tucson, Arizona. The authors analyzed 1,511 observations over an average followup period of 8.8 years in 353 subjects aged 5.5 to 25 years. The last available lung function value (as residuals after regressing the data with different power functions of age and height) was used as outcome. Residuals for vital capacity were significantly higher among subjects aged 14 years or less at entry whose mothers smoked cigarettes (mean = +3.3 vs. -1.4 among nonexposed subjects, $p < 0.001$). Parental smoking had no direct effect on outcome FEV_1 or $V_{max}50\%$, but showed significant interactions with personal smoking and parental history of airway obstructive diseases in their effects on $V_{max}50\%$; subjects who had started smoking or whose parents had airway obstructive diseases and were exposed to ETS had the lowest $V_{max}50\%$ residuals at the end of followup.

In subsequent reports, Lebowitz and Holberg (1988) and Tager and coworkers (1987) reanalyzed two sets of longitudinal pulmonary function data: the one on which the preceding study from Tucson, Arizona, was based (Lebowitz et al., 1987) and data for children of similar age from East Boston, Massachusetts (Tager et al., 1983). The objective was to determine if the different answers with regard to the effect of maternal smoking (significant for the Boston study; no effect for the Tucson study) were due to the use of different statistical tools. Applying the same multivariable analysis of covariance for both data sets, Lebowitz and Holberg (1988) confirmed the positive effect of maternal smoking of $FEF_{25-75\%}$ with the data from Boston ($p < 0.05$) and the lack of a significant effect of maternal smoking on $V_{max}50\%$ with the data from Tucson, Arizona. A first-order autoregressive model applied by Tager and collaborators (1987) to both data sets showed effects of maternal smoking on FEV_1 with the Boston data but not with the Tucson data. The authors concluded that the most likely factor responsible for the disparate results was the exposure difference in the two populations.

Tsimoyianis and collaborators (1987) compared the prevalence of low levels of $FEF_{25-75\%}$ (< 70% of predicted) in athletes exposed and unexposed to ETS (for more information on this study see Section 7.5.1). Of 132 exposed athletes, 18 (13.6%) had low $FEF_{25-75\%}$ compared with 2 of 61 (3.3%) unexposed athletes (OR = 4.7; 95% C.I.= 1.1, 20.8).

Kauffmann and collaborators (1989b) assessed familial factors related to lung function in a cross-sectional study of 1,160 French children. Levels of lung function (FEV_1 and $FEF_{25-75\%}$) were significantly lower in children with mothers who smoked when compared to those whose mothers were nonsmokers. The authors reported a loss of 10 mL of FEV_1 ($p < 0.05$) and of 15 mL/s of $FEF_{25-75\%}$ ($p < 0.01$) for every gram of tobacco smoked per day by the mother. These associations were independent of sex, town of origin, age, height, weight, and intrafamilial aggregation of lung function. There was no effect of paternal smoking on lung function.

Chan and coworkers (1989b) performed lung function tests in a cohort of 130 children of low birthweight (under 2,000 grams) at 7 years. These authors had previously reported on the respiratory outcome of these same children (see Section 7.5.1). Children of low birthweight whose mothers smoked had significantly lower values of percentage of predicted $V_{max}75\%$ than did low-birthweight children whose mothers did not smoke (80.7% vs. 91.4%, $p < 0.01$). This association was independent of sex, birthweight, neonatal respiratory illness, and treatment. As 92% and 79% of mothers who smoked when the child was 7 years old were smokers before and during their pregnancy, respectively, it was not possible to determine whether the effect of maternal smoking was fetal or postnatal.

The study by Dijkstra and collaborators (1990) has been described earlier (Section 7.5.1). The authors studied, together with respiratory symptoms, lung function and its relationship with indoor exposures to ETS and nitrogen dioxide in a population of 634 Dutch children 6 to 12 years of age. When compared with unexposed children, children exposed to ETS had significantly lower levels of FEV_1 (−1.8%; 95% C.I. = −0.2, −3.3), $FEF_{25-75\%}$ (−5.2%; 95% C.I. = −1.4, −8.8) and Peak Flow (−2.8%; 95% C.I. = −0.6, −4.8). Adjustment for smoking by the mother when she was pregnant with the investigated child removed little of the effect of current ETS exposure on lung function. The authors suggested that this indicated that the associations seen at ages 6 to 12 years were not just mirroring harm that was caused when the children were exposed in utero to tobacco smoke components inhaled by the mother. There was no association between exposure to NO_2 and lung function.

A previously mentioned study by Strachan and coworkers (1990) (Section 7.5.1) included lung function measurements in 757 children. Lung function variables were adjusted for sex, height, and housing characteristics. The authors found a significant negative correlation between salivary cotinine concentrations and levels of $FEF_{25-75\%}$ ($p < 0.05$) and $V_{max}75\%$ ($p < 0.05$). For these indices, the difference between adjusted mean values for the top and bottom quintiles of salivary cotinine was of the order of 7% of the mean value in the children with undetectable levels.

The longitudinal study by Martinez and coworkers (1992) has been reviewed earlier (Section 7.6.1). In addition to their findings on incidence of childhood asthma, these authors reported that, at the end of followup, children of mothers with 12 or fewer years of formal education and who smoked 10 or more cigarettes per day had 15% lower mean values for percentage of predicted $FEF_{25-75\%}$ than did children of mothers of the same level of education who were nonsmokers or smoked fewer than 10 cigarettes per day. Maternal smoking had no effect on percentage of predicted $FEF_{25-75\%}$ values in children of mothers who had at least some education beyond high school. Female children of smoking mothers ($\geq$ 10 cig./day) had 7%

higher vital capacity than did female children of mothers who were nonsmokers or light smokers (< 10 cig./day), and this was independent of maternal education. All differences were still significant after controlling for parental history of respiratory disease.

7.8.2. Summary and Discussion on Pulmonary Function in Children

This report concludes that there is a causal relationship between ETS exposure and reductions in airflow parameters of lung function (FEV_1, $FEF_{25-75\%}$, $V_{max}50\%$, or $V_{max}75\%$) in children. For the population as a whole, these reductions are small relative to the intraindividual variability of each lung function parameter; for $FEF_{25-75\%}$, for example, reductions range from 3% to 7% of the levels seen in unexposed children, depending on the study analyzed. Groups of particularly susceptible or heavily exposed subjects have larger decrements: Exposed children of low birthweight, for example, had 12% lower $V_{max}75\%$ than did children of similar birthweight who were not exposed to ETS (Chen, 1989). Likewise, children of less educated mothers who smoked 10 or more cigarettes per day were shown to have 15% lower mean $FEF_{25-75\%}$ than children of less educated mothers who did not smoke or smoked fewer than 10 cigarettes per day. This stronger effect may be explained by Strachan and coworkers' (1989) finding that children of lower socioeconomic status have higher salivary cotinine levels, for any amount of parental smoking, than do children of higher socioeconomic status.

The studies reviewed suggest that a continuum of exposures to tobacco products starting in fetal life may contribute to the decrements in lung function found in older children. In fact, exposure to tobacco smoke products inhaled by the mother during pregnancy may contribute significantly to these changes, but there is strong evidence indicating that postnatal exposure to ETS is an important part of the causal pathway.

New longitudinal studies have demonstrated that young adults who were exposed earlier in life to ETS are also more susceptible to the effects of active smoking (Lebowitz et al., 1987). In addition, Sherrill and collaborators (1990) showed, in a longitudinal study, that children who entered a longitudinal study with lower levels of lung function still had significantly lower levels later in life. The high degree of tracking shown by these spirometric parameters implies that the decrements in lung function related to passive smoking may persist into adulthood. Although the subsequent rates of decline in lung function of these subjects have yet to be studied in detail, the findings by Sherrill and coworkers (1990) support the idea proposed by the Surgeon General's report (U.S. DHHS, 1986) that, by the mechanisms described above, passive smoking may increase the risk of chronic airflow limitation.

7.9. PASSIVE SMOKING AND RESPIRATORY SYMPTOMS AND LUNG FUNCTION IN ADULTS

Both the NRC report (1986) and the Surgeon General's report (U.S. DHHS, 1986) extensively reviewed the evidence then available on involuntary smoking and respiratory health in adults. The Surgeon General's report concluded that healthy adults exposed to ETS may have small changes on pulmonary function testing but are unlikely to experience clinically significant deficits in pulmonary function as a result of exposure to ETS alone. The report added that the small magnitude of the effect implied that a previously healthy individual would not develop chronic lung disease solely on the basis of ETS exposure in adult life. It was suggested that small changes in lung function may be markers of an irritant response, possibly transient, to the irritants known to be present in ETS.

The NRC report concluded that it was difficult to document the extent to which a single type of exposure like ETS affects lung function. The report attributed this difficulty to the large number of factors, including other exposures, that affect lung function over a lifetime. The report added that results in adults should be evaluated for possible misclassification of ex-smokers or occasional smokers as nonsmokers, as well as possible confounding by occupational exposures to other pollutants. The authors of the report considered it "unlikely that exposure to ETS can cause much emphysema" (page 212), but that, "as one of many pulmonary insults, ETS may add to the total burden of environmental factors that become sufficient to cause chronic airway or parenchymal disease" (page 212).

7.9.1. Recent Studies on Passive Smoking and Adult Respiratory Symptoms and Lung Function

Six recent studies of respiratory symptoms and lung function in adults are presented in Table 7-11.

Svendsen and collaborators (1987) studied longitudinal data from 1,245 married American men aged 35 to 57 years who reported that they had never smoked. Subjects who had smoking wives had significantly higher mean levels of exhaled carbon monoxide (7.7 vs. 7.1 ppm, $p < 0.001$) but not of serum thiocyanate. These men also had lower levels of age- and height-adjusted FEV_1 (mean difference = 99 mL; 95% C.I. = 5, 192.4 mL). However, those with wives who smoked 20 or more cigarettes per day had higher mean adjusted FEV_1 (3,549 mL) than those with wives who smoked 1 to 19 cigarettes per day (3,412 mL), whereas nonexposed subjects had mean adjusted FEV_1 of 3,592 mL.

Kalandidi and coworkers (1987) studied 103 Greek ever-married women aged 40 to 79 who were admitted in 1982 and 1983 to a hospital in Athens with obstructive or mixed type reduction of pulmonary function, without improvement after bronchodilatation. The women

Table 7-11. Recent epidemiologic studies on the effects of passive smoking on adult respiratory symptoms and lung function

Authors	Population studied	ETS exposure assessment	Outcome variable	Results[1]	Observations
Svendsen et al. (1987)	1,245 married American nonsmoking men aged 35 to 57 yr.	Subject's report of spouse's smoking habits	FEV_1	Mean difference of 99 mL (5-192 mL)	No dose-response effect
Kalandidi et al. (1987)	103 Greek women with obstructive lung disease aged 40 to 79 yr.; 179 control women; all nonsmokers	Subject's report of spouse's smoking habits	See population studied	OR = 1.9 (1.0, 4.0)	No dose-response effect
Masi et al. (1988)	636 subjects aged 15 to 36 yr.	Subject's report of exposure to ETS	Maximal expiratory flows (MEF); diffusing capacity (DC)	Inverse relationship with ETS exposure at home in men for MEF; with exposure at work in women for DC	Strongest effect in men for exposure before age 17 yr.
Kauffmann et al. (1989a)	2,220 American women aged 25 to 69 yr.; 3,850 French women aged 25 to 59 yr.	Subject's report of spouse's smoking habits	Self-report of respiratory symptoms; lung function	OR = 1.3 for wheezed in U.S. sample; OR = 1.4 for cough and OR = 1.2 for dyspnea in French sample; lower FVC and FEV_1 ($p=0.01$) in French women age ≥40 yr.	Increased risks for respiratory symptoms did not reach statistical significance

(continued on the following page)

Table 7-11. (continued)

Authors	Population studied	ETS exposure assessment	Outcome variable	Results[1]	Observations
Hole et al. (1989)	7,997 subjects aged 45 to 64 yr. in Scotland	Questionnaires answered by household members	Cardiorespiratory symptoms; lung function	No significant increase in risk of symptoms; decrease in FEV_1 (60 mL) when a cohabitee smoked >15 cig./day	
Schwartz and Zeger (1990)	100 student nurses in Los Angeles, California	Questionnaire answered by subject on presence of a smoking roommate	Respiratory symptoms assessed by self-administered questionnaire	Increased risk of having phlegm (OR = 1.4 [1.1, 1.9])	Over-reporting by exposed subjects may bias results

[1]95% confidence intervals in parentheses.

denied that they had ever been smokers, and their husbands' smoking habits were compared with those of 179 ever-married controls of the same age selected from visitors to the hospital. Patients were 1.9 times more likely to have smoking spouses than were controls (95% C.I. = 1.0, 4.0). However, odds ratios were higher for women whose spouses smoked 20 or fewer cigarettes per day (2.5) than for those whose spouses smoked more than 20 cigarettes per day. The unusually high number of nonsmoking women hospitalized with chronic lung disease in a 2-year period suggests that some could have severe asthma unresponsive to bronchodilators and that the results could in part illustrate exacerbation of symptoms in asthmatic women exposed to ETS.

Masi and coworkers (1988) mailed questionnaires to 818 subjects aged 15 to 35 who had previously performed detailed lung function testing and carboxyhemoglobin (COHb) measurements. A total of 636 subjects responded to the questionnaire, and 293 denied having smoked regularly before the date of the lung function tests. All but five subjects had COHb values below 5 grams %. Questionnaires assessed past and present ETS exposure, both at home and at work. Indices of cumulative exposure to ETS at home and at work were calculated from the number of reported smokers on each location, the smoking conditions reported for each area, and the number of years of exposure. In men, there were significant inverse relationships between cumulative exposure to ETS in the home and maximal expiratory flows at low lung volumes. A more detailed analysis showed that in these subjects, exposure before 17 years of age had the strongest effects on lung function, whereas exposure in the 5 years preceding the lung function tests had no effect on lung function. Exposure at work significantly decreased the diffusing characteristics of the lung in women.

Kauffmann and collaborators (1989a) compared the results obtained from a parallel analysis of the association of passive smoking with respiratory symptoms and lung function in 2,220 American women aged 25 to 69 years and 3,855 French women aged 25 to 59 years. Women were classified according to their personal and current spouse's smoking habits. After adjusting for age, city of origin, educational level, and occupational exposure, ever-passive-smokers (excluding active smokers) had significantly more wheeze than true never-smokers (i.e., never active and with nonsmoking spouse) in the U.S. sample (OR of approximately 1.3; C.I. cannot be calculated). There was a positive trend for French passive smokers to have more chronic cough (OR = 1.4) and dyspnea (OR = 1.2), but both results could be due to chance (95% C.I. = 0.8, 2.4 and 0.9, 1.6, respectively). In both samples, no significant decrease of lung function was observed for passive smokers compared with true never-smokers in the whole sample, although FEV_1/FVC values for ever-passive-smokers tended to be intermediate between those of true never-smokers and ex-smokers or active smokers. French women aged 40 or older who were passive smokers had

significantly lower FVC ($p < 0.01$) and FEV_1 ($p < 0.01$) than did true never-smokers, but no such effect was seen among American women of the same age.

Hole and coworkers (1989) studied cardiorespiratory symptoms and mortality in a cohort of 7,997 subjects aged 45 to 64 and followed for 11 years in urban west Scotland. A self-administered questionnaire was used in 1972-76 to assess respiratory symptoms and active smoking by each member of the household. When compared with true never-smokers (i.e., persons who were not active smokers and did not live with an active smoker), passive smokers were invariably at a higher risk of having each cardiorespiratory symptom examined (including infected sputum, persistent sputum, and dyspnea), but all 95% confidence intervals for odds ratios included 1. FEV_1 (adjusted for sex, age, and height) was significantly higher in true never-smokers than in passive smokers ($p < 0.01$), but this effect was mainly due to the low adjusted FEV_1 of passive smokers with high exposure (i.e., exposed to a cohabitee who smoked > 15 cig./day; mean = 1.83 L) when compared with those with low exposure (mean = 1.89 L) or with no exposure (mean = 1.88 L). This study was initiated when there was little concern for the possible ill effects of passive smoking and is based on self-reports of active smoking by cohabitees. It is thus probably not affected by classification bias due to overreporting of symptoms by smokers.

Schwartz and Zeger (1990) studied data from a cohort of approximately 100 student nurses in Los Angeles who kept diaries of acute respiratory symptoms (cough, phlegm, and chest discomfort) and for whom data on exposure to passive smoking and air pollution were available. After controlling for personal smoking, a smoking roommate increased the risk of an episode of phlegm (OR = 1.4; 95% C.I. = 1.1, 1.9) but not of cough. The authors also excluded asthmatics (on the assumption that medication could bias the results) and found that in this case, the odds ratio of having phlegm increased to 1.8 (95% C.I. = 1.3, 2.3). The greater sensitivity of diaries of acute symptoms such as those used herein, compared with the indices of period prevalence of symptoms used in other studies, may have increased the power of this study. However, overreporting by exposed subjects is still a possible source of bias in a study that is solely based on self-report of symptoms.

7.9.2. Summary and Discussion on Respiratory Symptoms and Lung Function in Adults

Recent studies have confirmed the conclusion by the Surgeon General's report (U.S. DHHS, 1986) that adult nonsmokers exposed to ETS may have small reductions in lung function (approximately 2.5% lower mean FEV_1 in the studies by Svendsen et al. [1987] and Hole et al. [1989]). Using modern statistical tools designed for longitudinal studies, new evidence also has emerged suggesting that exposure to ETS may increase the frequency of respiratory symptoms

in adults. These latter effects are estimated to be 30% to 60% higher in ETS-exposed nonsmokers compared to unexposed nonsmokers.

Because active smoking causes significant reductions in lung function and significant increases in prevalence of respiratory symptoms (U.S. DHHS, 1984), the reported effects of passive smoking in adults are biologically plausible. From a quantitative point of view, effects of passive smoking on lung function are approximately comparable to those reported for light (< 10 cig./day), male active smokers (Camilli et al., 1987). However, because of the self-selection of smokers and other factors, it is difficult to make direct quantitative comparisons between the effects of active and passive smoking. The process of self-selection is likely to occur among smokers by which more susceptible individuals never start smoking or quit smoking early in life (the "healthy smoker" effect). Therefore, lower lifetime doses may be required to elicit effects among nonsmokers than among smokers. The different nature of ETS and MS also has been discussed in previous chapters and must be taken into account when comparing effects of active and passive smoking.

Several sources of bias and confounding factors need to be considered in studies of the effects of single exposures in adults. Classification bias due to underreporting of active smoking or past smoking may significantly affect the results of these studies. Because there is marital aggregation of smoking (i.e., smokers tend to marry smokers, and nonsmokers are more prone to marry nonsmokers), this source of misclassification is more probable among spouses of smokers and may introduce differential biases in some studies. The resulting small overestimation of effect may be nevertheless substantial for effects that are particularly subtle, such as those described for ETS exposure in adults. In addition, recent public concern with passive smoking may increase the awareness of respiratory symptoms in exposed subjects, who may be thus more prone to report symptoms than are unexposed subjects. Studies using objective measures of lung function obviously are not affected by the latter type of bias.

Adults are exposed to multiple sources of potentially harmful substances during their lifetimes, and it is not always possible to control for the effects of these substances because they often are unknown or unmeasurable. In general, the majority of these exposures should introduce nondifferential error to the studies, which would lead to underestimates of the true effects. For example, a significant nondifferential error may be introduced by ETS exposure during childhood, which is known to cause decrements in lung function (see Section 7.7) that may be carried into adulthood. ETS exposure during childhood also is known to cause childhood respiratory diseases (see Sections 7.3, 7.5, and 7.6). Such childhood respiratory diseases, whatever the cause, also may be reflected in decreased respiratory health in adulthood. These effects have

not been accounted for in the studies of ETS exposure and lung function in adults, but it is likely that they would lead to underestimates of the ETS effects in the adult studies.

Conversely, effects of ETS would be overestimated if a certain noxious exposure were more likely to occur among ETS-exposed subjects. In this sense, social factors need to be accurately controlled, because prevalence of smoking is significantly higher among less educated than among higher educated subjects (Pierce et al., 1989). Most reviewed studies have controlled for indices of socioeconomic level in a satisfactory manner. Finally, lifestyles may differ between spouses of smokers and those of nonsmokers, but it is not possible to determine a priori the effect of this confounder on the relationship between passive smoking and respiratory health.

The influence of these factors and sources of bias, together with the subtlety of the effects, may explain the inconsistent and sometimes contradictory results of the studies reviewed in this report. In fact, such variability should be expected, particularly for studies with relatively low power (i.e., low probability of finding a statistically significant difference when a difference really exists). The lack of a dose-response relationship in some studies also may be explained by the multiplicity of uncontrolled factors that may affect lung function.

In summary, recent evidence suggests that passive smoking has subtle but statistically significant effects on the respiratory health of nonsmoking adults.

8. ASSESSMENT OF INCREASED RISK FOR RESPIRATORY ILLNESSES IN CHILDREN FROM ENVIRONMENTAL TOBACCO SMOKE

In the preceding chapter, a review was presented of recently published studies regarding the association between respiratory illnesses in children and environmental tobacco smoke (ETS) exposure. The biological plausibility and the possible pathogenetic mechanisms involved in each group of illnesses included in the chapter also were discussed. The purpose of this chapter is to consider the weight of the evidence as a whole, to analyze in detail possible sources of systematic bias or confounding that may explain the observed associations, and to estimate the population impact of ETS-associated respiratory illnesses.

8.1. POSSIBLE ROLE OF CONFOUNDING

In the review of the available evidence indicating an association (or lack thereof) between ETS exposure and the different outcomes considered in this report, the possible role of several confounding factors was analyzed in detail (see Chapter 7). Such analysis will only be summarized here.

- Other indoor air pollutants (wood smoke, NO_2, formaldehyde, etc.) have not been found to explain the effects of ETS but may interact with it to increase the risk of both respiratory illnesses and decreased lung function in children.
- Many of the studies reviewed in this report and in those of the National Research Council (NRC, 1986) and the Surgeon General (U.S. DHHS, 1986) used either multivariate statistical methods of analysis or poststratification of the sample to control for the possible confounding effects of socioeconomic status. Others controlled for this effect by study design. It can be concluded that socioeconomic status does not explain the reported effects of ETS on children's health, although children belonging to some social groups may be at an increased risk of suffering the effects of passive smoking (see also Section 8.3).
- The effect of parental symptoms on the association between ETS and child health also has been extensively analyzed. It can be concluded that, although parents with symptoms may be more aware of their children's symptoms than are parents without symptoms, it is unlikely that this fact by itself explains the association. In fact, objective parameters of lung function, bronchial responsiveness, and atopy, which are not subject to such sources of bias, have been found to be altered in children exposed to ETS.

- The effects of passive smoking may be modified by several characteristics of the exposed child. Increased risk has been reported in premature infants and infants of low birthweight, infants who are not breast-fed, infants who are kept at home with smoking mothers and not sent to day-care centers, asthmatic children, and children who are active smokers.
- Maternal smoking during pregnancy has significant effects on fetal growth and development and may affect lung growth as well as the immunologic system. However, reports of important effects of paternal smoking on the child's health and studies in which ETS exposure was found to have effects that were independent of in utero exposure indicate that maternal smoking during pregnancy does not explain the relation between passive smoking and child health, but modifies the effects of ETS.

In summary, there are no single or combined confounding factors that can explain the observed respiratory effects of passive smoking in children.

8.2. MISCLASSIFICATION OF EXPOSED AND UNEXPOSED SUBJECTS

The importance of misclassification of exposed and unexposed children has not been addressed and will be analyzed in detail below.

Two possible sources of systematic bias related to subject misclassification are considered. The first is upward bias from the effect of active smoking in children; the second is downward bias due to misreporting and background exposure. Both have also been considered in the assessment of ETS and lung cancer in adults. Adjustment for background exposure will be similar to that presented in Chapter 6, except that data for increased incidence of some ETS-associated respiratory diseases show some evidence of thresholds that must also be taken into account.

8.2.1. Effect of Active Smoking in Children

The possibility needs to be considered that some children may be smokers themselves and that this may happen more often among children of smoking parents than among those of nonsmoking parents. This would bias the results upwards or against the null effect. This source of bias is only applicable to studies of older children; regular active smoking may occur but is rare before early adolescence. A study of third graders in Edinburgh, Scotland, by Strachan and coworkers (Strachan et al., 1989, see Section 7.4.1, for example) showed that salivary cotinine levels compatible with active smoking were found in 6 of 770 children ages 6-1/2 to 7-1/2 years, suggesting only a small potential for bias. Consideration should also be given to the fact that some

of the effects described in Chapter 7 (for example, the increased risks for acute respiratory illnesses [Section 7.3] and for cough, phlegm, and wheezing [Section 7.5]) have been found to be stronger in younger children (i.e., those less likely to be active smokers) than in older children. This observed reduced effect with increasing age may be in part due to an age-related increase in misclassification of exposed subjects as "unexposed" (see below), but it is clear that these specific effects of ETS *do not increase with age*, as would be expected if active smoking biased the results of studies of ETS effects in older children. It can thus be concluded that the association between respiratory health in children and ETS is not attributable to active smoking by some children. It has been suggested that active and passive smoking may interact to increase the effects of either exposure separately (Lebowitz and Holberg, 1988). This interaction is biologically plausible, because it is likely that active smoking may be more harmful in children whose lungs have been previously affected by ETS (see Section 7.1).

8.2.2. Misreporting and Background Exposure

Various investigators have measured cotinine levels in body fluids in infants and children and correlated the results with parental reports of ETS exposure. Coultas and coworkers (1987) reported that 37% of children under 5 years of age whose parents were nonsmokers had a salivary cotinine level greater than 0, compared with 32% of children ages 6 to 12 and with 35% of children ages 13 to 17. These authors did not ask parents to report possible sources of ETS exposure for their children other than their own tobacco consumption. Strachan and coworkers' study in 6-1/2- to 7-1/2-year-old children in Scotland (Strachan et al., 1989) showed that 73% of children from households with no smokers had detectable concentrations of cotinine in saliva, whereas only 1 in 365 children from households with one or more smokers had no detectable salivary cotinine. The assay used by Strachan and coworkers was 10 times more sensitive than that used by Coultas and coworkers, and this may explain the larger number of subjects with detectable levels in the former study when compared with the latter.

Greenberg and coworkers (1984) studied cotinine levels in 32 infants in North Carolina with reported exposure to tobacco smoke within the previous 24 hours and in 19 unexposed infants. All subjects were under 10 months old. Urine samples of all exposed infants contained cotinine, whereas all unexposed infants except 2 (11%) had undetectable urine cotinine or levels below those of exposed infants with the lowest levels of urine cotinine. This same group of researchers reported results for a larger sample (433 infants at a mean age of 18 days) of the same population (Greenberg et al., 1989). They found that, of 157 infants who reportedly lived in nonsmoking households and were also not in contact with smokers the previous week, 37 infants

(24%) had cotinine in their urine. They concluded that these infants had contact with tobacco smoke during the previous week and that this contact was unknown to or was not reported by their mothers.

Greenberg and coworkers (1991) followed 152 of the 433 infants originally enrolled and reassessed exposure to ETS (through maternal interviews) and urine cotinine levels when the child was 12.3 ± 0.6 months old. They found a significant increase in the prevalence of tobacco smoke absorption, indicated by excretion of cotinine, during the first year of life (from 53% at a mean age of 3 weeks to 77%). The interviews showed that this was mainly due to an increased exposure to nonhousehold sources of smoke (from 14% to 36%). The proportion of infants who reportedly had no contact with smokers but had cotinine in their urine increased from 24% at 3 weeks to 49% at 1 year of age.

These results indicate that studies relying exclusively on parental questionnaires to ascertain ETS exposure in children may misclassify many exposed subjects as nonexposed. Moreover, the degree of misclassification may increase with the child's age.

The possible consequences of this misclassification of exposure need to be discussed in detail. Nondifferential misclassification (i.e., exposure classification that is incorrect in equal proportions of diseased and nondiseased subjects) biases the observed results toward a conclusion of no effect (Rothman, 1986). The effect of differential misclassification depends on the direction in which misclassification occurs. If true ETS exposure is preferentially reported by parents of diseased subjects (i.e., there is reporting bias), an excess of disease prevalence would be found among exposed subjects when compared with unexposed subjects that is unrelated to any biological effect of ETS. The evidence available clearly indicates that this is a very unlikely explanation for the reported misclassification of ETS exposure in infants and children. In fact, reporting bias cannot explain the substantial increase in "underreporting" of exposure with age. The logical explanation is provided by the finding that exposure to nonhousehold smokers increases significantly with age and parallels the increase in the proportion of subjects who have cotinine in their urine (Greenberg et al., 1991). There is no reason to believe that exposure to smokers may occur preferentially among diseased children, and the contrary may be more reasonable; the increased awareness of the ill effects of ETS inhalation may induce parents to limit contact between their diseased children and nonhousehold smokers. Thus, the net effect of misclassification of exposure, both nondifferential and differential, should be a systematic downward bias or bias toward observing no effect. A correction for the nondifferential misclassification bias of background exposure is made in Section 8.3.

8.3. ADJUSTMENT FOR BACKGROUND EXPOSURE

An important conclusion of the previous discussion is that studies based on parental questionnaires may underestimate the health risk from ETS in children due to underreporting of ETS exposure. The NRC (1986) report on passive smoking adopted the use of cotinine measures to correct for misreporting of ETS exposure for lung cancer effects, and this approach was adapted for use in Chapter 6 of this report. It will also be employed here, with the cotinine ratios, however, based on exposure data in children rather than in adults. The method is based on several assumptions: (1) cotinine concentrations in body fluids of nonsmokers are linearly related to ETS exposure, (2) the excess risk of respiratory illness in subjects exposed to ETS is linearly related to the dose of ETS absorbed, (3) the relationship between ambient and absorbed ETS is linear, and (4) one cotinine determination may adequately represent average childhood exposure to ETS.

As support for assumptions 1 and 2, three recent studies have used body cotinine levels as biomarkers for ETS exposure in children. All three have found significant associations between cotinine levels and respiratory effects in children. Etzel et al. (1992) found a significant relationship between serum cotinine levels and otitis media with effusion for children who attended a day-care facility during the first 3 years of life. Ehrlich et al. (1992), in a study that used questionnaires on maternal caregiver smoking as well as urinary cotinine levels to assess ETS exposure, found that by either measure ETS exposure was significantly associated with both acute and nonacute asthma in children. Furthermore, urinary cotinine levels in asthmatic children showed a highly significant correlation with maternal caregiver smoking status. In the third study, Reese et al. (1992) found urinary cotinine levels significantly ($p < 0.02$) elevated in children admitted to the hospital with bronchiolitis compared with a group of similarly aged children admitted with nonrespiratory illnesses. There was also a highly significant correlation ($p < 0.0005$) between urinary cotinine levels and maternal smoking as determined by questionnaire. Thus, the evidence suggests that questionnaire ascertainment of childhood exposure to ETS and cotinine biomarkers in children are highly correlated with each other and that both correlate with childhood diseases. This information is used to develop the risk assessment models below.

While considerable evidence exists for assumptions 1 through 3 (see also Chapter 3), there is some evidence that assumption 4 may not be entirely warranted, at least for older children. Coultas and coworkers (1990b), in a small study of 9 children from 10 homes with at least 1 smoker, reported that there is considerable variability in cotinine levels in body fluids within individuals exposed to ETS when such levels are repeatedly measured on different days. However, Henderson et al. (1989), doing repeated urinary cotinine measures in preschool children, found stable levels over 4 weeks. Thus, while the method of adjustment is based on group mean

body cotinine levels, which apparently reflect household ETS levels well, the intraindividual variability, at least in older children, may subject these means to some error.

Application of the method proposed by the NRC requires some knowledge of Z, the ratio between the operative mean dose level in the "exposed" group, d_E, and the mean dose level in the "unexposed" group, d_N. $RR(d_E)$, the relative risk for the group identified as "exposed" compared with the group identified as "unexposed," is thus given by

$$RR(d_E) = (1+Z^*\beta d_N)/(1+\beta d_N) \qquad (8\text{-}1)$$

where β is the amount of increase per unit dose and $Z > RR(d_E) > 1$. (The "unexposed" group actually contains those with background exposure plus those truly unexposed.)

Several studies are available that could be used for the purpose of estimating Z. Jarvis and coworkers (1985) studied 569 nonsmoking schoolchildren ages 11 to 16 in Great Britain. The investigators reported that, when compared with salivary cotinine levels in children of nonsmoking parents (N = 269), mean levels of salivary cotinine were 3.0 times as high in children whose father smoked (N = 96), 4.4 times as high in children whose mother smoked, and 7.7 times as high in children whose parents were both smokers. Pattishall and coworkers (1985) reported that children from homes with smokers (N = 20) had 4.1 times as high mean levels of serum cotinine as children from nonsmoking families. Black children in the same study, however, had lower values of Z (2.8) than did white children. Coultas and coworkers (1987) found that, among 600 U.S. children up to age 17 years, mean salivary cotinine levels were between 1.3 and 2.6 times as high among subjects exposed to one cigarette smoker at home as among unexposed subjects, and between 2.9 and 3.5 times as high among subjects exposed to two or more smokers at home as among subjects not exposed to cigarette smokers at home. Strachan and coworkers (1989) reported separate results for 6-1/2- to 7-1/2-year-old Scottish children belonging to families living in their own homes and for those belonging to families living in rented homes. In the former, geometric mean salivary cotinine was 6 times as high among subjects exposed to one cigarette smoker at home as among unexposed subjects and 16 to 17 times as high among subjects exposed to two or more smokers at home as among unexposed subjects. For children belonging to families living in rented homes, the same ratios were 3 to 5.5 times and 4 to 7 times, respectively.

While these studies show consistent relationships between mean body cotinine levels in children and home smoker occupancy, there is also a wide variability in the estimated Z ratios, ranging from 1+ to 17. These different estimates may have very important effects on the background exposure adjustment and, thus, on the calculation of adjusted relative risks for

different studies (see also Chapter 6). For example, for a study in which the observed relative risk (RR) is 2.0 but for which the Z ratio is 3, equation 8-1 can be solved for βd_N, which is the estimated increase in relative risk for the group called "unexposed" but who in fact have been exposed to some recent ETS. Solving, $\beta d_N = 1$. Thus, the adjusted RR for the group identified as "unexposed" would be 2, and the adjusted RR for an "exposed" group compared with a truly unexposed group would be $1 + (3*1) = 4$, i.e., twice the observed risk. For a similar example (observed RR = 2) but with $Z = 5$, $\beta d_N = 0.3$, the RR for a group identified as "unexposed" in this case would be 1.3, and the adjusted RR for an "exposed" to a truly unexposed group would be 2.67. Finally, if the observed RR is still 2 but $Z = 17$, $\beta d_N = 0.07$, RR for "unexposed" would be 1.07 and the adjusted RR for exposed children would be 2.13. These results are shown in Table 8-1.

These calculations show that when use of parental questionnaires significantly underestimates their children's exposures to other sources of ETS (other than via the parental ETS) and values of Z are lower (as found in black children by Pattishall and coworkers [1985], and in children of lower socioeconomic status by Strachan and coworkers [1989]), the "true" RR of children exposed to ETS may be considerably underestimated. But perhaps the most important conclusion that may be derived from the above analysis is that exposure to ETS from sources other than smoking parents may be high enough to constitute a significant risk for their health. This may be particularly consequential for children of lower socioeconomic levels, whose nutritional status, crowded conditions at home, and opportunity for contact with biological agents of disease make them a part of the population that is particularly susceptible to respiratory illnesses during infancy and childhood. Available data show that ETS exposure via nonhousehold members in these children, as measured by cotinine levels in body fluids, may be as much as one-third that of children exposed to one smoking parent ($Z = 3$). In the example presented above (observed RR = 2), the estimate of the adjusted relative risk is 4 for children of smoking parents to the truly unexposed children. However, using the same assumptions, children of *nonsmoking parents* who are exposed to ETS (at background levels found in some of the studies) would have twice as high a risk of developing the illness under study as children truly unexposed to ETS.

A cautionary note about the model is appropriate. Table 8-1 shows that, for observed RR = 2 and $Z = 3$, the adjusted relative risk is 4. However, as the observed RR and Z get closer together, the behavior of the model becomes erratic. This is shown in Table 8-2. In fact, the model (equation 8-1) becomes undefined if Z is less than or equal to the observed RR, and it reaches some stability only as Z becomes at least 30% to 50% greater than the RR.

Table 8-1. Adjusted relative risks for "exposed children." Adjusted or background exposure based on body cotinine ratios between "exposed" and "unexposed" and equation 8-1

		Z Ratio of body cotinine levels ("exposed"/"unexposed")							
		1.50	2.00	3.00	5.00	7.00	10.00	13.00	17.00
Observed Relative Risks (RR)	1.0	1	1	1	1	1	1	1	1
	1.50	-	3.00	2.00	1.71	1.64	1.59	1.57	1.55
	1.75	-	7.00	2.80	2.15	2.00	1.91	1.87	1.84
	2.00	-	-	4.00	2.67	2.40	2.25	2.18	2.13
	2.50	-	-	10.00	4.00	3.33	3.00	2.86	2.76
	3.00	-	-	-	6.00	4.50	3.86	3.60	3.43

Table 8-2. Behavior variations in adjusted relative risks from equation 8-1 when the observed relative risks and Z ratios are close together

		Z ratio							
		1.50	1.75	2.00	2.25	2.50	2.75	3.00	10.00
Observed Relative Risks (RR)	1.50	-	4.50	3.00	2.50	2.25	2.10	2.00	1.59
	1.75	-3.5	-	7.00	4.38	3.50	3.06	2.80	1.91
	2.00	-2.0	-6.00	-	10.00	6.00	4.67	4.00	2.25
	2.25	-1.5	-3.38	-9.00	-	13.50	7.88	6.00	2.62
	2.50	-1.25	-2.50	-5.00	-12.50	-	17.50	10.00	3.00

Fortunately, the estimates of Z presented above are appreciably greater than the observed relative risk estimates seen in Chapter 7, and in the observed range of both RR and Z, the model yields relatively stable estimates of the adjusted RR. Furthermore, as discussed in Chapter 6, the values of RR and Z are expected to be correlated for each study, i.e., the greater the Z ratio between exposed and unexposed groups in each study, the greater should be the observed RR and the less the effect of the (equation 8-1) adjustment.

If the above model is correct, then exposure of children to ETS other than at home (parental smoking) may be an important risk factor for respiratory illness in childhood. On the other hand, it is also possible that for at least some respiratory illnesses, outside exposure to ETS has relatively little effect, either because outside exposures in younger children tend to be less than those of older children or because there may be a threshold of exposure below which certain respiratory effects may not be expected to occur. For this latter case, equation 8-1 is not an appropriate model, and the observed relative risk would be taken to be the true risk. Both models are addressed in the sections that follow.

8.4. ASSESSMENT OF RISK

Neither the NRC report (1986) nor the Surgeon General's report (U.S. DHHS, 1986) attempted to assess the population or public health impact of the increased risk of respiratory disorders in children attributable to ETS exposure. In this section, estimates will be derived for the number of ETS-attributable lower respiratory tract infections in infants and for the induction and exacerbation of childhood asthma. Quantifying the public health impact of other conditions, such as reduced lung function, coughing, wheezing, and middle ear effusion, is difficult, either because of the lack of overt symptoms or because some necessary U.S. population health statistics are not available. Estimates of sudden infant death syndrome (SIDS) occurrences attributable to ETS will not be made but will be discussed in Section 8.4.3.

For the following quantitative analyses, estimates will be developed in terms of ranges. The ranges are derived by the use of both threshold and nonthreshold (equation 8-1) models, different estimates for population incidence and prevalence, and estimated values of Z and RR from studies reviewed above. Various differences in design, disease definition, and conduct among these studies make them less adaptable to meta-analysis techniques than were the lung cancer studies. To the extent that a less rigorous statistical analysis is attempted here, the ranges should reflect that uncertainty.

8.4.1. Asthma

From the analysis of studies regarding risk for asthma and ETS exposure, it was concluded that passive smoking increases both the number and severity of episodes in asthmatic children. It was further concluded that ETS is a risk factor for new cases among previously asymptomatic children, since the evidence is suggestive, but not conclusive, of a causal association (see Section 7.6). Relative risks for asthma ranged from 1.0 to 2.5 in the studies analyzed, but methodologies differed considerably among studies, and effects were often found only in children of mothers who smoke heavily. Of the four large studies, totaling more than 9,000 children (Burchfield et al., 1986; Sherman et al., 1990; Weitzman et al., 1990; Martinez et al., 1991b), three showed statistically significant risk estimates ranging from 1.7 to 2.5, with the two largest ratios, 2.5 (Martinez et al., 1991b) and 2.1 (Weitzman et al., 1990), coming from comparisons using children of heavily smoking mothers ($\geq$ 10 cig./day) as the exposed group. The third study (Burchfield et al., 1986) had OR = 1.7 for males with two smoking parents, but results were not significant either for girls or for children with one parental smoker. The fourth study (Sherman et al., 1990) (770 children) did not find an effect, but made no effort to assess the effect of heavy smoking by parents, nor was there control for socioeconomic status. Thus, assigning a range of 1.75 to 2.25 for the estimated relative risk of developing asthma for children of mothers who smoke 10 or more cigarettes per day appears reasonable and is within the ranges of observed risk.

The above results suggest two possible scenarios. One scenario is that relatively heavy exposure to ETS is needed to bring on asthma, i.e., there is a threshold of exposure below which effects will not occur. Alternatively, lesser exposures may merely induce fewer effects, not detectable statistically with these study designs. The choice of scenario does not affect the observed relative risk but will affect whether or not an adjustment for background exposure (Z ratio) is appropriate. Under the first (threshold) scenario, the estimates of RR = 1.75 to 2.25 need no adjustment; under the alternative (nonthreshold) scenario, equation 8-1 applies.

Considering the nonthreshold model first, from the discussion in Section 8.3, it can be assumed that values of 3 to 10 may be a reasonable range for estimates of Z (i.e., the ratio of body cotinine levels in children whose mothers smoke heavily to those of children whose mothers do not smoke). Lower values of Z would yield significantly larger estimates of asthma cases attributable to ETS. Based on the above estimates for a range of Z and RR and use of the nonthreshold model, the estimated range of adjusted relative risks for children of mothers who smoke 10 or more cigarettes per day would be approximately 1.91 to 6.00 (see Table 8-3). Transforming relative risks to

Table 8-3. Range of estimates of adjusted relative risk and attributable risk for asthma induction in children based on both threshold and nonthreshold models, and different values for Z.

	Threshold model[1]		Nonthreshold model[2]				
Observed relative risk	1.75	2.25	1.75	2.25	1.75	2.00	2.25
Z = Cotinine ratio (exposed/unexposed)	-	-	10	10	3	3	3
Adjusted relative risk[3]	-	-	1.91[4]	2.62[4]	2.80[5]	4.00[5]	6.00[5]
AR_E[6]	0.43	0.56	0.48	0.62	0.64	0.75	0.83
AR_T[7] (P_I[8]=0.17)	0.07	0.09	-	-	-	-	-
AR_T (P_I[9]=0.26)	-	-	0.12	0.16	0.17	0.20	0.22
ETS-attributable population impact[10]	8,000 to 20,000	10,000 to 26,000	13,000 to 34,000	18,000 to 45,000	19,000 to 46,000	22,000 to 54,000	24,000 to 60,000

[1]Threshold model assumes that heavy ETS exposure (i.e., mothers smoking ≥ 10 cig./day) is required to induce new cases.
[2]Nonthreshold model assumes that all ETS exposure can produce some new cases of asthma.
[3]Equation 8-1 for the nonthreshold model; no adjustment for the threshold model.
[4]Ratio of mean body cotinine levels: Z = 10.
[5]Ratio of mean body cotinine levels: Z = 3.
[6]Attributable risk fraction for the exposed population.
[7]Attributable risk fraction for the total (mixed) population.
[8]Proportion of women of reproductive age who smoke at least 10 cigarettes per day (0.26 × 0.65).
[9]Proportion of women of reproductive age who smoke cigarettes.
[10]Range based on 2 million to 5 million asthmatic children under 18 years old in the United States, and assumes that the number of ETS-attributable new cases at each age is constant.

attributable risks (Rothman, 1986), 48% to 83% of all cases of asthma among children of mothers who smoke 10 or more cigarettes per day may be attributable to passive smoking based on

$$AR_E = 100 * (1 - [1/RR]) \quad (8\text{-}2)$$

where AR_E is the attributable risk (%) for the exposed population.

Under the assumptions of the threshold model, RR = 1.75 to 2.25 for children of heavily smoking mothers, and the AR_E = 43% to 56% (see Table 8-3); for children of light-smoking mothers, RR = 1 and the AR_E = 0.

To calculate the percentage of all cases occurring in a mixed population of exposed and unexposed individuals that is attributable to exposure (AR_T), knowledge of the prevalence of mothers smoking 10 or more cigarettes per day is needed because

$$AR_T = AR_E * P_I \quad (8\text{-}3)$$

where P_I is the proportion of cases that is exposed (Rothman, 1986). It has been reported that approximately 26% of the population of women of childbearing age smoked in the United States in 1988 (CDC, 1991b) and in 1990 (CDC, 1992b). For the number of cigarettes smoked, Weitzman and coworkers (1990), using the 1981 National Health Information Survey (NHIS), found that approximately 50% of smoking mothers of children ages 0 to 5 years smoke 10 or more cigarettes per day. The 1990 NHIS reports that 78% of smoking women ages 18 to 44 smoke at least 10 cigarettes per day (data courtesy of Dr. Gary Giovino, CDC). We have used an average of 65% to derive the estimates in Table 8-3. Based on these figures and the threshold model, it can thus be estimated that approximately 7% to 9% of all cases of asthma may be attributable to exposure to ETS from mothers who smoke 10 or more cigarettes per day. Estimates of the prevalence of asthma among U.S. children less than age 18 vary from 5% to 10% (Clark and Godfrey, 1983) to 3% to 8% (R. Evans et al., 1987), depending on disease definition. This latter paper uses the data from the 1979-1981 NHIS and derives a population asthma prevalence of 2 million to 5 million. A more recent estimate from the 1989 NHIS is 3.9 million (U.S. DHHS, 1990b). Use of these population prevalence figures and the threshold model provides a range of 8,000 to 26,000 as the annual number of new cases of childhood asthma attributable to mothers who smoke 10 or more cigarettes per day. The confidence in this estimate is medium and is dependent on the conclusion that ETS is a risk factor for asthma induction.

If the nonthreshold model applies, use of the same prevalence figures leads to a range of 13,000 to 60,000 new cases per year attributable to all ETS exposures (Table 8-3).

While the range of 8,000 to 60,000 is plausible, the existing data are more supportive of the threshold model, which assumes that rather heavy exposures to ETS are required to induce asthma in previously asymptomatic children (Section 7.6.2). Thus, the range of 8,000 to 26,000 will be adopted as the more probable range of new cases among children per year attributable to ETS exposure.

In view of the increased number and severity of asthmatic episodes also caused by ETS, the public health impact of ETS on asthmatic children is considerably greater than the range of estimates for new cases presented above. Shephard (1992), after reviewing several studies, concludes that ETS exposure (from any source) exacerbates preexisting asthma in approximately 20% of patients. If this figure is correct, up to 1 million asthmatic children could be affected. Also, in an earlier study, O'Connell and Logan (1974) found that parental smoking aggravated clinical symptoms of 67% of 265 asthmatic children in the Midwest versus 16% of 137 controls ($p < 0.0001$) and that 10% of 400 asthmatic patients (of both smoking and nonsmoking parents) considered tobacco smoke a major aggravating factor. D. Evans and coworkers (1987) found that passive smoking by asthmatic children in New York City (via presence of smokers in the household) was associated with a mean annual increase of 1.34 emergency room visits per year for asthmatic symptoms, an increase of 63% over asthmatic children from nonsmoking households. Ehrlich et al. (1992), in a study not reviewed by Shephard (1992), found that asthmatics with clinically significant symptoms had both higher cotinine levels than controls ($p = 0.04$) and an OR = 2.0 ($p = 0.03$) for maternal caregivers who smoke. Using this estimate of 2.0 with equation 8-1 and a $Z = 3$ also leads to an attributable risk fraction, AR_T, of 20% (equation 8-3). Multiplying this 20% by the 2 million to 5 million asthmatic children in the United States yields estimates of 400,000 to 1,000,000 whose condition is aggravated by exposure to ETS. Thus, exposure to ETS in general and especially to parental ETS adversely affects hundreds of thousands of asthmatic children.

8.4.2. Lower Respiratory Illness

From the assessment of available data (see Section 7.3), it was concluded that exposure of infants and young children to ETS causes an increased incidence of lower respiratory illness (LRI). An examination of the data in the referenced studies of both Tables 7-1 and 7-2 leads to the conclusion that the observed risk of having LRIs is approximately 1.5 to 2.0 times as high in young children whose mothers smoke as in those whose mothers do not smoke and that the risk is probably higher in infants than in toddlers.

This estimate is also consistent with that of the NRC (1986), which estimated a relative risk of up to 2 for infants who have one or more parents who smoke. The more recent evidence

reviewed here strongly suggests that the increased risk due to ETS exposure lasts for at least the first 18 months and decreases after that. Based on this evidence, this chapter estimates a relative risk range of 1.5 to 2.0 for infants and children up to 18 months old who have smoking mothers. It will assume that the increased risk is zero after 18 months.

Based on these findings, and following equation 8-1 with a range of Z = 3 to 10 and RR = 1.5 to 2.0, the adjusted relative risk range becomes 1.6 to 4.0, and AR_E takes the range 38% to 75%. As in the previous section, for equation 8-3, the mixed population attributable risk AR_T takes the range 10% to 20%, again based on 1988 and 1990 estimates of approximately 26% women of childbearing age who smoked (CDC, 1991b, 1992b). Because the estimated mean number of cigarettes smoked by these women is approximately 17 to 20 per day (CDC 1991b, 1992b), it is reasonable to assume that most children of smoking mothers will be exposed. Therefore, the proportion of cases exposed, P_I, is estimated to be 0.26.

It has recently been shown that the incidence of LRIs early in life is approximately 30% (Wright et al., 1991). When the analysis is limited to the first 18 months of life, the population at risk is approximately 5.5 million children. A slight modification of the same algorithms described above yields 150,000 to 300,000 cases of LRIs annually in children under 18 months old attributable to exposure to ETS generated mostly by smoking mothers. For RR = 1.5 and Z = 10, the attributable risk fraction for the exposed population, AR_E, is 0.38, and the attributable risk fraction for the total population, AR, is 0.10. Assuming 3.7 million children less than 1 year old and a 30% incidence of LRI, the ETS-attributable population risk is 110,000. In order to get the incidence rate for the 1.8 million children aged 12 to 18 months, also with 30% incidence, the 110,000 must be subtracted from the 540,000 before multiplying by 0.10. The product of 43,000 is then added to 110,000 to determine the total annual incidence of 150,000 LRIs. For RR = 2.0 and Z = 3 the total annual incidence is about 300,000. Approximately 5% of these LRIs require admission to a hospital (Wright et al., 1989); therefore, it is estimated that 7,500 to 15,000 hospitalizations yearly for LRIs may be attributable to ETS exposure.

While these estimates may appear large, three factors suggest that they are on the low side. First, although these estimates are calculated only for children less than 18 months old, Section 7.3 presents evidence that these ETS-attributed increased risks extend at a decreasing rate up to 3 years of age. Second, no estimates have been calculated for exposure in a smoking father-nonsmoking mother household. Third, these numbers do not take into account the fact that many infants and young children have recurrent LRIs, and therefore, more than one episode of such illnesses may be attributable to ETS in each exposed child.

8.4.3. Sudden Infant Death Syndrome

Because this report concludes that there is an association between maternal smoking and SIDS but is unable to determine the contribution that ETS makes to that association (see Section 7.7), no estimate of ETS-attributable SIDS deaths will be calculated. The Centers for Disease Control (CDC, 1991a) provides an estimate of 702 SIDS deaths attributable to maternal smoking, based on a relative risk of 1.5 for infants of actively smoking mothers. While this report concurs with the numbers and the methodology used to determine that estimate, it is unable to apportion the in utero, lactation, and ETS exposure components of the risk.

8.5. CONCLUSIONS

This chapter has attempted to estimate the impact on the U.S. population of ETS exposure on childhood asthma and lower respiratory tract infections in young children. For new cases of asthma in previously asymptomatic children under 18 years of age, we estimate that 8,000 to 26,000 is a probable range of new cases per year that are attributable to ETS exposure from mothers who smoke at least 10 cigarettes per day. The confidence in this range is medium and is dependent on the conclusion that ETS is a risk factor for asthma induction.

While the data are most supportive of a situation in which heavy exposures to ETS are required to induce new cases of asthma, two other scenarios would lead to larger estimates. The first is that even in the absence of smoking mothers, a child could receive heavy ETS exposure from other sources. The second is that lesser ETS exposures induce fewer numbers of new cases, and the increase is not statistically detectable. Under this latter (nonthreshold) scenario, the range of new cases of asthma annually attributable to ETS exposure is 13,000 to 60,000.

This report concludes that, in addition to inducing new cases of asthma, ETS exposure increases the number and severity of episodes among this country's 2 million to 5 million asthmatic children. This chapter considers exposure to parental smoking to be a major aggravating factor to approximately 10%, or 200,000, asthmatic children. Estimates of the number of asthmatics whose condition is aggravated to some degree by ETS exposure are very approximate but could run well over 1 million.

This chapter also estimates that 150,000 to 300,000 cases annually of lower respiratory tract infections in children up to 18 months old are attributable to ETS exposure, most of which comes from smoking parents (mostly mothers). These ETS-attributable cases are estimated to result in 7,500 to 15,000 hospitalizations annually. Confidence in these estimates is high based on the conclusion of a causal association and the strong validity of parental smoking as a surrogate of temporally relevant ETS exposure in infants and young children. Additional cases and

hospitalizations are expected to occur in children up to 3 years old in decreasing numbers, but this report makes no further quantitative estimates.

Infants' exposure to ETS may also be responsible for a portion of the more than 700 deaths from SIDS attributable to maternal smoking by the CDC (1991a), but this report is unable to determine whether and to what extent these deaths can be attributed specifically to ETS exposure.

The estimates of population impact presented above are given in ranges and approximate values to reflect the uncertainty of extrapolating from individual studies to the population. As with the lung cancer population impact assessment (Chapter 6), these extrapolations are all based on human studies conducted at true environmental levels. Therefore, they suffer from none of the uncertainties associated with either animal-to-human or high-to-low exposure extrapolations.

In addition to the estimates presented above, ETS exposure in children also leads to reduced lung function, increased symptoms of respiratory irritation, and increased prevalence of middle ear effusion, but this report does not provide estimates of the population impact of ETS exposure for these conditions.

APPENDIX A

REVIEWS AND TIER ASSIGNMENTS FOR EPIDEMIOLOGIC STUDIES OF ETS AND LUNG CANCER

ADDENDUM: PERTINENT NEW STUDIES

Several pertinent studies on the respiratory health effects of passive smoking have appeared since the cutoff date for inclusion in this report. The studies are cited here for the benefit of anyone who may wish to follow up on these topics. The studies are briefly described below, and the authors' conclusions are presented. We do not formally review these studies in this report, and the citations do not represent a full literature search. These new studies are generally consistent with this report's conclusions that environmental tobacco smoke (ETS) exposure increases the risk of lung cancer in nonsmokers and affects the respiratory health of infants.

Two of the new studies are case-control studies of ETS and lung cancer in U.S. female nonsmokers (Stockwell et al., 1992; Brownson et al., 1992). Stockwell et al. conclude that "long-term exposure to [ETS] increases the risk of lung cancer in women who have never smoked." Similarly, Brownson et al. conclude, "Ours and other recent studies suggest a small but consistent increased risk of lung cancer from passive smoking."

In an autopsy study of Greeks who had died of causes other than respiratory diseases, Trichopoulos et al. (1992) found an increase in "epithelial, possibly precancerous, lesions" in the lungs of nonsmoking women who were married to smokers. The authors concluded that their results "provide support to the body of evidence linking passive smoking to lung cancer. . . ." In a fourth study, a case-control study of ETS exposure and lung cancer in dogs, Reif et al. (1992) found an association between lung cancer and exposure to a smoker in the home for breeds with short- and medium-length noses. These results are not statistically significant, and the authors characterize their findings as "inconclusive."

Finally, Schoendorf and Kiely (1992) conducted a case-control analysis of sudden infant death syndrome (SIDS) and maternal smoking status (i.e., maternal smoking both during and after pregnancy [combined exposure], maternal smoking only after pregnancy [passive exposure], and no maternal smoking). These investigators conclude that their data "suggest that both intrauterine and passive tobacco exposure are associated with an increased risk of SIDS."

ADDENDUM REFERENCES

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APPENDIX A. REVIEWS AND TIER ASSIGNMENTS FOR EPIDEMIOLOGIC STUDIES OF ETS AND LUNG CANCER

A.1. INTRODUCTION

This appendix contains material that is used in Section 5.5, entitled *Analysis by Tier and Country*. As described in that section, each study is individually reviewed and assigned to one of four tiers based on its assessed utility for the objective of evaluating the evidence of an association between environmental tobacco smoke (ETS) exposure and incidence of lung cancer. The means of constructing study reviews is described in the next section, followed by a description of the scheme for scoring studies on various items and then assigning the studies to tiers according to the outcome. The final section of this appendix contains the individual study reviews and the tier numbers assigned to them.

A.2. CONSTRUCTION OF INDIVIDUAL STUDY REVIEWS

Descriptions of the four prospective cohort studies are individualized according to the requirements of each study. Reviews of case-control studies follow a structured format, consisting of three parts: (1) the author's abstract, which summarizes the most salient features and conclusions in the author's opinion; (2) a study description based on the contents of a completed study form designed around principles of good epidemiologic practice and issues specific to environmental tobacco smoke; and (3) a section of comments related to evaluation and interpretation of the study. The study reviews are used to assign studies to tiers according to the procedure described in Section A.3.

The review form for case-control studies shown in Section A.2.1 was completed for each case-control study in order to systematically extract information about characteristics of interest for preparation of the reviews. The form was an aid in treating study reviews uniformly and noting omissions or incomplete discussion on issues that may affect the potential for bias or confounding.

The study descriptions in Section A.4 were then prepared by following the outline and information in the completed forms. Some items included in the form pertain to characteristics that would apply to a case-control study on any topic, i.e., they are "generic items" related to principles of good epidemiologic investigation; the remaining items tend to identify areas of potential bias specific to the topic of ETS and lung cancer.

A.2.1. Review Form for Case Control Studies

PART I. GENERAL

Study name_____

Location_____

Time period (data collection)_____

Study objective(s)_____

_____

_____

The source of the primary data set is the current study _____ or a parent study

(ref)_____

containing CS (current)_____ FS (former) _____ NS (never-smoker) _____

Study uses term "nonsmoker" _____ or "never-smoker" _____ to mean

nonsmoker_____

_____

never-smoker_____

_____

"Exposed" to ETS means (preferably in terms of spousal smoking)

_____

_____

Recall span (how far back in time ETS exposure was measured)_____

_____

ETS sources include cigarette _____ cigar _____ pipe _____ other _____

Describe inclusion of nonsmoking (never-smoking) females not currently married (number of cases and controls, assumptions regarding exposure)

_____

_____

_____

II. DATA COLLECTION (includes NS_____ FS_____ CS_____ unless noted)

Inclusion/exclusion criteria

Cases_____

_____

_____

Controls (include matching variables in PART V)_____

_____

_____

Main source of subjects	Cases	Controls
Hospital(s) #_____	_____	_____
Community	_____	_____
Other_____	_____	_____

Incident cases Y_____ N_____

Control sampling

Cumulative _____ Density _____

Unmatched _____ Matched _____

Method of collection	Cases	Controls
Face-to-face	_____	_____
Telephone	_____	_____
Self-admin. ques.	_____	_____
Medical records	_____	_____
Vital stat. records	_____	_____
Other_____	_____	_____

Collected data verified/corroborated with other sources Y_____ N_____

	Cases	Controls
Sample size (prior to attrition)		
females	_____	_____
males	_____	_____
Attrition (selection or followup)		
females	_____	_____
males	_____	_____

Source of response

subject	_____	_____
proxy	_____	_____

Exposure sources NS_____ FS_____ CS_____

	Yes	No
Childhood	_____	_____
Adulthood	_____	_____
Spouse	_____	_____
Parents/in-laws	_____	_____
Other family/ live-ins	_____	_____
Workplace	_____	_____
Other	_____	_____

Age NS_____ FS_____ CS_____

Distribution	Cases	Controls
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
Mean	_____	_____
Standard error	_____	_____
Standard deviation	_____	_____
Range	_____	_____

PART III. CLINICAL DATA

Primary lung cancer verified by NS_____ FS_____ CS_____

Histology	_____
Cytology	_____
Radiology/clinical	_____
Death certificate	_____
Tumor registry	_____
Mortality records	_____
Other_____	_____
Not verified	_____

Airway proximity (no. exp cases/no. cases) NS_____ FS_____ CS_____

Central _____

Table_____

Peripheral _____

Tumor type (no. exp cases/no. cases) NS_____ FS_____ CS_____

Squamous cell _____

Table_____

Small cell _____

Adenocarcinoma _____

Large cell _____

Others or unspecified _____

PART IV. STATISTICAL ANALYSIS (includes NS_____ FS_____ CS_____ unless noted)

Raw data (for analysis)		Cases	Controls
females	unexp	_____	_____
	exp	_____	_____
males	unexp	_____	_____
	exp	_____	_____

Comments (include measure of exposure) Table _____

Unadjusted (crude) analysis

Estimate OR _____ _____% CI (_____,_____)

Comments Table _____

Test of signif. p-value _____

Test for trend p-value _____

Comments Table _____

Adjusted analysis

Estimate OR _____ _____% CI (_____,_____)

Test of signif. p-value _____

Test for trend p-value _____

Comments Table _____

PART V. DEPENDENT VARIABLES (potential confounders and effects modifiers considered)

	In Matching	In Analysis	Otherwise
Age			
Gender			
Race/ethnicity			
Hospital			
Residence/ neighborhood			
Housing type			
House/room sizes			
Vital statistics			
Smoking status			
SES			
Medical health			
Menstrual/ reproductive			
Occupation			
Outdoor air pollution			
Cooking habits			
Drinking			
Diet			
Education			
Family history of lung cancer			
Other indoor smoke/fumes			
Radon			
Lifestyle			
Climate/ ventilation			

A.3. TIER CLASSIFICATION SCHEME

The items and study scores used in the algorithm to calculate tier numbers are given in Table A-1. The items and scoring system in that table and the algorithm for converting the scores to a tier number are the topics of this section.

The items displayed in the headings of Table A-1 will be described after explanation of how assignments are calculated from the numbers in that table. Positive values in the table are

unfavorable (penalty points); a blank entry means the item was not a problem; negative values are favorable (bonus points) and occur in a few instances where the study performed well above the norm indicated by a blank, e.g., FONT, KOO, and HOLE(Coh) each have an entry of "-0.5" under "Less than 90% confirmation by histology or cytology" in Category C for particularly high attention given to confirming primary lung cancer in subjects classified as cases. Bonus scores are always -0.5 and are assigned somewhat sparingly as they have the potential to cancel penalty scores and thus mask a study weakness. Parentheses around an entry indicate that the penalty points were assigned due to insufficient information (so there is effectively a penalty imposed if the information needed was not included in the source). The asterisk that occurs under the item "unsuitable indoor environment" is a marker that automatically places the study into Tier 4 under the assignment rule to be described next (the unsuitable environment refers to high levels of coal smoke in all instances).

Tier numbers for each study are calculated from the entries in Table A-1 as follows. Totals are calculated by category and across all items, as shown in Table A-2. If the total for each category is less than 2.5, then the tier assignment is determined as follows:

Total Score	Tier
1.75 or less	1
2.00 - 3.75	2
4.00 - 5.75	3
6.00 or greater	4

The value 2.5 is designated as a cutoff point for each category. If a study has one or more category totals greater than or equal to 2.5, the tier classification is increased by 1 (i.e., 1 is added to the tier number shown in the above table if any category totals are 2.5 or greater). The three studies conducted in regions of China where indoor air is heavily polluted with smoke from burning coal, denoted by an asterisk under item "unsuitable indoor environment," are placed in Tier 4 (see reviews in Section A.4 for GENG, LIU, and WUWI). The resultant assignment of studies to tiers is shown in Table A-2.

A scheme that attempts to assess utility and to numerically rank studies accordingly, as done here, has a high degree of subjectivity. Different analysts would be apt to disagree about elements of any such approach and the appropriate weights for those elements in assigning studies to tiers, as suggested above. One of the difficulties is that the significance of a study "weakness" is difficult to assess. For example, the use of proxy respondents may be a source of bias, but the direction and magnitude of bias are unknown for any given study. Thus, one is faced with rating studies largely on the basis of one's ability to ascertain what study features are significant and

Table A-1. Study scores for tier assignments

	Category A		Category B		
Study	Former smokers included	Smoking status unverified	Exposure criteria questionable	Exposure of unmarrieds	Exposure status unverified
AKIB					-0.5
BROW			1	(0.5)	
BUFF			1.5		
CHAN			2	(0.5)	
CORR				0.5	
FONT		-0.5			-0.5
GAO			1.5	0.5	
GARF			0.5	0.5	
GENG	1		1		
HUMB	0.5				
INOU	1		1		
JANE					
KABA	0.5		1		
KALA					
KOO					
LAMT	0.5				
LAMW					
LEE					
LIU			1		
PERS		-0.5			
SHIM					
SOBU					
SVEN					
TRIC	1				
WU				0.5	
WUWI	1				
BUTL(Coh)					
GARF(Coh)			1		
HIRA(Coh)	0.5				
HOLE(Coh)					

(continued on the following page)

Table A-1. (continued)

Study	Category C		Category D	
	Secondary lung cancers possible	Less than 90% confirm. histol./cytol.	Less than 90% face-to-face	Unblinded interviews
AKIB		1	0.5	
BROW				
BUFF				
CHAN	0.75	0.5		
CORR				(0.5)
FONT		-0.5		(0.5)
GAO		0.5		(0.5)
GARF				
GENG				
HUMB		0.5		
INOU	0.75	(0.5)		(0.5)
JANE				0.5
KABA				
KALA		0.5		(0.5)
KOO		-0.5		
LAMT				
LAMW				(0.5)
LEE	0.75	(0.5)		0.5
LIU	0.75	1		
PERS			0.5	
SHIM			0.5	(0.5)
SOBU			0.5	(0.5)
SVEN			1	0.5
TRIC		1		0.5
WU			1	0.5
WUWI		0.5		0.5
BUTL(Coh)			0.5	
GARF(Coh)	0.5	1	0.5	
HIRA(Coh)	(0.5)	0.5		
HOLE(Coh)	(0.5)	-0.5		

(continued on the following page)

Table A-1. (continued)

Study	Category E		Category F (Cohort Only)	
	More than 10% proxy respondents	Uneven proxy response distribution	Change in smoking or ETS status	More than 10% loss to followup
AKIB	1			
BROW	1	0.75		
BUFF	1			
CHAN	0.75			
CORR	0.5			
FONT	0.5			
GAO				
GARF	1.5			
GENG				
HUMB	1	0.75		
INOU	1			
JANE	0.5			
KABA				
KALA				
KOO				
LAMT				
LAMW				
LEE	0.5			
LIU				
PERS	(0.5)			
SHIM				
SOBU				
SVEN				
TRIC				
WU				
WUWI				
BUTL(Coh)			0.5	
GARF(Coh)			0.5	0.75
HIRA(Coh)			0.5	
HOLE(Coh)			0.5	(0.5)

(continued on the following page)

Table A-1. (continued)

Study	Category G (Case-control only)		
	Unsuitable indoor environment	Smoking-related disease in controls	Nonincident cases included
AKIB			0.5
BROW			(0.5)
BUFF			
CHAN		0.75	
CORR			0.5
FONT			
GAO			
GARF		0.75	(0.5)
GENG	*		
HUMB			
INOU		0.75	(0.5)
JANE			
KABA			
KALA			
KOO			
LAMT			
LAMW			
LEE			
LIU	*		
PERS			
SHIM		0.75	(0.5)
SOBU		0.75	
SVEN		0.5	
TRIC			
WU			
WUWI	*		
BUTL(Coh)			
GARF(Coh)			
HIRA(Coh)			
HOLE(Coh)			

(continued on the following page)

Table A-1. (continued)

Study	Category H		
	Uncontrolled for age	Uncontrolled for other factors	Problem(s) with stat. methods
AKIB			
BROW	1.5		0.5
BUFF	1.5		
CHAN	1.5		
CORR	1.5		
FONT		0.5	
GAO		1	
GARF			
GENG	1.5	1	
HUMB			
INOU			
JANE			1
KABA	1.5		
KALA			
KOO			1
LAMT	1.5		
LAMW	1.5	1	
LEE			
LIU	1.5	1	
PERS			
SHIM	1.5		
SOBU		1	
SVEN			
TRIC	1.5		
WU			1
WUWI		1	
BUTL(Coh)		1	
GARF(Coh)			
HIRA(Coh)			
HOLE(Coh)			

Table A-2. Total scores and tier assignment

Study	Category A	B	C	D	E	F	G	H	Total	Tier Assign.
AKIB		-0.5	1	0.5	1		0.5		2.5	2
BROW		1.5			1.75		0.5	2.0	5.75	3
BUFF		1.5			1			1.5	4.0	3
CHAN		2.5	1.25		0.75		0.75	1.5	6.75	4
CORR		0.5		0.5	0.5		0.5	1.5	3.5	2
FONT	-0.5	-0.5	-0.5	0.5	0.5			0.5	0	1
GAO		1.5	0.5	0.5				1.5	4.0	3
GARF		1			1.5		1.25		3.75	2
GENG	1	1					*	2.5	4.5	4
HUMB	0.5		0.5		1.75				2.75	2
INOU	1	1	1.25	0.5	1		1.25		6.0	4
JANE				0.5	0.5			1	2.0	2
KABA	0.5	1						1.5	3.0	2
KALA			0.5	0.5					1.0	1
KOO			-0.5					1	0.5	1
LAMT	0.5							1.5	2.0	2
LAMW				0.5				2.5	3.0	3
LEE			1.25	0.5	0.5				2.25	2
LIU		1	1.75				*	2.5	5.25	4
PERS	-0.5			0.5	0.5				0.5	1
SHIM				1			1.25	1.5	3.75	2
SOBU				1			0.75	1	2.75	2
SVEN				1.5			0.5		2.0	2
TRIC	1		1	0.5				1.5	4.0	3
WU		0.5		1.5				1	3.0	2
WUWI	1		0.5	0.5			*	1	3.0	4
BUTL(Coh)				0.5		0.5		1	2.0	2
GARF(Coh)		1	1.5	0.5		1.25			4.25	3

(continued on the following page)

Table A-2. (continued)

Study	Category A	B	C	D	E	F	G	H	Total	Tier Assign.
HIRA(Coh)	0.5		1			0.5			2.0	2
HOLE(Coh)						1			1.0	1

*Unsuitable indoor environment

some quantitative construct reflecting an opinion of their relative importance. Additionally, there is the possibility of misinterpreting the source or of the omission of needed information from the source. A further limitation is the inability to include all features of all studies that might affect one's judgment of it.

Reservations notwithstanding, the heterogeneity of the ETS studies in objectives and characteristics of design, data collection, analysis, and interpretation make it worthwhile to classify studies according to some evaluation of their utility for assessing ETS and lung cancer. The items used for scoring studies are described in the remainder of this section. The descriptions are written in the language of case-control studies (references to "cases," "controls," etc.). Where cohort studies are evaluated (end of Table A-1), the equivalent concept for cohort studies is applied under each category heading, with exceptions as noted in the text. An "ideal" is described for each item, to give the scores a reference point. The ideal applies to the needs of this report, however, and not to what may have been the ideal for the individual study objectives.

Very few of the studies were designed and executed with the sole, or even primary, objective of this report. Consequently, high penalty scores or an unfavorable tier assignment indicating limited utility for our objectives should not be interpreted as low study quality relative to the purpose for which the study was conducted. Comments included on the likely direction of bias refer to bias of the relative risk estimate. "Upward bias" is an expected excess in the observed relative risk above its true (but unknown) value (which is 1.0 if the null hypothesis of no effect is correct). "Downward bias" refers to bias in the opposite direction. "Bias toward the null hypothesis" is used sometimes in the text. It refers to an influence on the observed relative risk toward 1.0, the value of the true relative risk when the null hypothesis is correct. When the true relative risk exceeds 1, "bias toward the null" and "downward bias" are interchangeable. The probable magnitude of bias is more difficult to ascertain than the likely direction of bias. The

relative values of the penalty scores under items in Table A-1 reflect our judgment on this issue. To determine why a specific study was scored with penalty or bonus points on any particular item, the reader needs to refer to the review of that study in Section A.4. A description of items in Table A-1 follows.

Category A: Never-Smoker Status

- Inclusion of former smokers. The ideal is for all subjects to be true never-smokers. Inclusion of subjects who report themselves as never-smokers but who are actually current smokers causes an upward bias in the relative risk (see Section 5.2.2 and Appendix B). Inclusion of former smokers may be a source of upward bias by similar arguments. Some degree of former smoking may be inconsequential depending on how much was smoked and the subsequent duration of abstinence, but this relationship is not well understood. Penalty points of 0.5 or 1 were assigned to studies that allowed some prior smoking because we view it as adding some degree of uncertainty compared with exclusive use of never-smokers as subjects.
- Verification of smoking status. The ideal is to implement all means available to verify the never-smoking status claimed by subjects. No studies were penalized on this item, but the few studies (i.e., FONT and PERS) that conducted thorough verification were given a bonus of -0.5.

Category B: ETS-Exposure Criteria

- Exposure criteria questionable. The ideal is for a female to be classified as ETS exposed according to a measure of duration (e.g., years of spousal smoking) and a measure of intensity (e.g., number of cigarettes smoked per day by the spouse). Of course, collecting data on measures of exposure is not meaningful unless it enters into the analysis. For the purpose of this report, the objective for case-control studies is to differentiate between subjects as sharply as possible on exposure to ETS using spousal smoking as an indicator. Knowledge is too limited to know how to accomplish this exactly, but extremes wherein the exposed group contains subjects with very little exposure or includes only subjects with very high exposure (while all lesser exposed subjects are classified as "unexposed") should bias results toward the null hypothesis. For cohort studies, GARF(Coh) was penalized because the duration of exposure to spousal ETS was limited.
- Exposure of unmarrieds. Ideally for this report, where the presence or absence of spousal smoking is emphasized as the main determinant of ETS exposure because of its

high commonality among studies, subjects would be female never-smokers whose history of exposure to spousal smoke has been reasonably constant over an extended duration (independent of whether a subject may have been married more than once). Studies vary in the extent to which this topic is considered and how it is handled, and assumptions may need to be considered in view of a country's social practices. For example, some studies classify women as unexposed to ETS while unmarried, which may be more reasonable in some cultures than others (e.g., probably more reasonable in Greece than in the United States). Biases resulting from this item are most commonly toward the null hypothesis.

- Verification of exposure status. The ideal is to verify statements regarding present and past exposure to ETS from spousal smoking from other sources. Two studies, AKIB and FONT, were given bonus points for extended efforts in that direction; no studies were penalized.

Category C: Lung Cancer Indication

- Secondary lung cancers possible. The ideal is assurance that all cases are accurately diagnosed with primary lung cancer and that cases are not included where the lung cancer may be secondary to another site. This item is closely related to the next one, which is concerned with the method of diagnosis/confirmation. Bias is toward the null hypothesis.
- Less than 90% confirmation by histology or cytology. The ideal is that the original diagnosis of lung cancer, or a confirmation of it, is conducted by histology. No penalty points are assigned, however, if at least 90% of the cases are diagnosed or confirmed by histology or cytology. Three studies, FONT, KOO, and HOLE(Coh), were given bonus points for extended efforts in diagnostic confirmation. The direction of bias is toward the null hypothesis.

Category D: Interview Type

- Less than 90% face-to-face interview. The ideal interviewing technique is face-to-face by trained interviewers. The effect on the quality of information from other types of data collection is unclear, but telephone interviews and mail-in questionnaires probably increase the rate of misclassification of subject information. The bias is toward the null hypothesis if the proportion of interviews by type is the same for cases and controls, and of indeterminate direction otherwise.

- Unblinded (case-control studies only). The ideal is for the interviewer to be unaware whether the subject is among the cases or controls and the subject to be unaware of the purpose and intended use of the information collected. Blinding of the interviewer is generally not possible in a face-to-face interview. In face-to-face and telephone interviews, potential bias may arise from the investigator's expectations regarding the relationship between ETS exposure and lung cancer incidence. The potential for bias is probably less with mail-in interviews.

Category E: Proxy Respondents

- More than 10% proxy respondents (10% of total for cohort studies and 10% of either total cases or total controls for case-control studies). The ideal is for data to be supplied by the subject because the subject generally would be expected to be the most reliable source. A subject may be either deceased or too ill to participate, however, making the use of proxy responses unavoidable if those subjects are to be included in the study (some studies appeared to exclude them). The direction and magnitude of bias from use of proxies is unclear, and may be inconsistent across studies.
- Uneven distribution between cancer/noncancer subjects. Ideally, the use of proxies is evenly distributed between cases and controls because this might be expected to minimize any net bias remaining from the use of proxy responses. The use of proxies is often much higher for cases than for controls, as one might expect. The effect of proxy distribution on bias is indeterminate.

Category F: Followup (Cohort Studies Only)

- Changes in smoking or ETS exposure not addressed. The ideal is for any changes in personal smoking status or exposure to spousal ETS to be recorded and taken into account in the analysis. If a subject begins active smoking during the course of the study, it may lead to upward bias (from arguments like those given for the effect of smokers who misreport themselves as never-smokers, as discussed in Section 5.2.2 and Appendix B); if the smoking status of the spouse changes, the likely bias would be toward the null hypothesis.
- More than 10% loss to followup. The ideal, of course, is zero loss to followup. The ideal is not achievable in practice, but it seems reasonable to expect loss to followup not to exceed 10%. The bias from loss to followup is indeterminate. Random loss may

have less effect than if subjects who are not followed up have some significant characteristics in common.

Category G: Design Issues

- Unsuitable indoor environment. The ideal indoor air environment contains no significant sources of pollution from nontobacco sources that likely contain one or more of the known or suspected carcinogens identified in tobacco smoke or would otherwise be expected to increase the incidence of lung cancer. The presence of high concentrations of indoor smoke from unvented or inadequately vented indoor combustion of coal for purposes of warmth or cooking is commonplace in some regions of China where studies were conducted. This condition is indicated in some studies and has been confirmed from other sources (see reviews in Section A.4 for GENG, LIU, and WUWI). It is expected that indoor coal smoke increases the level and variability of exposure to many of the same carcinogenic agents that occur in ETS, and therefore detection of an incremental increase in lung cancer incidence from ETS would be highly unlikely in such a setting.
- Smoking-related disease in controls (case-control studies only). The ideal is for controls to be free of any disease related to tobacco smoke. This is an issue in some studies where hospital controls are used. Potential bias is toward the null hypothesis.
- Nonincident cases included (case-control studies only). The ideal is for all cases to be incident (i.e., new cases that develop during an interval of time). A few studies began with prevalent cases and then proceeded with incident cases. The use of prevalent cases may introduce some bias of unknown direction because prevalence is affected by survival rate and lung cancer patients generally do not survive for an extended period. All studies scored on this item were given one-half point, which is in parentheses in most instances, indicating that information in the source is incomplete. Interview information must be obtained from surviving kin or other proxy subjects as well, but that issue is treated separately in a following item. Potential bias is of uncertain direction.

Category H: Analysis Issues

- Uncontrolled for age. The ideal is to control for age by matching on age in the design and then adjusting for age in the analysis of data. There is no clear formula for deciding which variables should be included in a matched analysis, and/or addressed in the analysis of the data collected. Age, however, is likely correlated with total

exposure for those classified as exposed to ETS and is suspected of playing a role in cancer etiology. The potential bias from age might be significant, but its likely direction and magnitude depend in an unknown way on the disparity of age distributions between cases and controls.

- Uncontrolled for other factors of importance. This item applies to studies that report an increased association of lung cancer with factors other than ETS exposure but do not consider further whether these factors may be confounders that should be controlled for in the analysis for ETS. For a variable to be a confounder of ETS, exposure to the variable and to ETS must be correlated (which determines the degree of confounding), and the association of the factor with lung cancer must be causal. The correlation should be readily calculable from the study data. Conclusions about causation may not be warranted, but one could still make the necessary calculations under the assumptions that they are causative and then report what implications causation (if correct) would have for the assessment of ETS. The expected effect from controlling for confounders is to move the estimated relative risk closer to the true value.
- Problem(s) with statistical methods. The ideal is that conclusions are drawn from the application of statistical methods that are appropriate to the problem and accurately interpreted. One penalty point was assigned studies where we took issue with the statistical methodology or results. The direction of bias is indeterminate, in general, as the situations differ between studies.

A.4. INDIVIDUAL STUDY REVIEWS

This section of Appendix A contains a review of each epidemiologic study based on the primary references listed in Table 5-1. Descriptions of the four prospective cohort studies are individualized according to the requirements of each study--for example, HIRA(Coh) has a long history of controversy in the literature, so the main arguments are chronicled and discussed as part of the review. As noted previously, reviews of case-control studies follow a structured format, consisting of three parts: (1) the author's abstract, which summarizes the most salient features and conclusions in the author's opinion; (2) a study description based on the contents of a completed study format designed around principles of good epidemiologic practice and features specific to ETS; and (3) a section of comments related to evaluation and interpretation of the study. The author's abstract is, of course, entirely the author's own words; the study description is intended to portray accurately the reference article vis-a-vis items in the study format, so the author's words

are used when possible; the comments section is entirely our own assessment of characteristics relevant to study interpretation and utility in this report.

An abstract only is available for the case-control study by Stockwell et al., (1991), referred to as STOC, which has not appeared in print yet. There is insufficient information on the study to include it in the main body of this report. Similarly, an abstract only is available for the second study of Kabat and Wynder (Kabat, 1990), which is included in an addendum following the review of their first study, KABA. The data for many of the studies reviewed have been extracted from a larger, more comprehensive study that includes active smokers. The subjects and their data used for investigation of an association between ETS exposure and lung cancer incidence are referred to as "ETS subjects" and "ETS data," respectively.

A.4.1. AKIB (Tier 2)

A.4.1.1. *Author's Abstract*

"A case-control study conducted in Hiroshima and Nagasaki, Japan, revealed a 50% increased risk of lung cancer among nonsmoking women whose husbands smoked. The risks tended to increase with amount smoked by the husband, being highest among women who worked outside the home and whose husbands were heavy smokers, and to decrease with cessation of exposure. The findings provide incentive for further evaluation of the relationship between passive smoking and cancer among nonsmokers."

A.4.1.2. *Study Description*

This community-based case-control study was conducted in Hiroshima and Nagasaki, Japan, in 1982. The data collected on passive smoking are part of a larger investigation of lung cancer among atomic bomb survivors, the principal objective of which is to evaluate the interactive roles of cigarette smoking and ionizing radiation. This article reports on married female never-smokers, an unmatched subset of the data from the whole study.

The whole study includes a total of 525 primary lung cancer cases diagnosed between 1971 and 1980. Cases were identified from the Hiroshima and Nagasaki Tumor and Tissue Registries and other records. Controls were selected from among the cohort members without lung cancer, two per case in Hiroshima and three per case in Nagasaki. The controls were individually matched to the cases with respect to year of birth (± 2 years), city of residence (Hiroshima or Nagasaki), sex, biennial medical examinations, and vital status. The majority of cases were deceased; those cases were matched to decedent controls by year of death (± 3 years), in addition to the other criteria. Controls were selected from causes of death other than cancer and chronic

respiratory disease. Face-to-face interviews were conducted for 81% (82%) of the eligible cases (controls), but 80% to 85% of the interviews for both cases and controls were actually conducted with the subject's next of kin. The mean age of cases at diagnosis is 72.1 years (range 36-94) for males and 70.2 (range 35-95) for females, which is high for lung cancer in Japan. Fifty-seven percent of the cases were pathologically confirmed; the remaining 43% were diagnosed by radiological or clinical findings.

ETS exposure in adulthood was assessed by spousal smoking status, including the average number of cigarettes smoked per day, age the spouse started smoking, and, for those who stopped smoking, the age at cessation. For childhood exposure, a single question was asked regarding whether the subject's mother or father or both smoked when the subject was living at home as a child; responses were obtained for only two-thirds of the subjects. No specific information on exposure to smoking by other household members' smoking or to smoking in the workplace was obtained. ETS exposure data were checked by comparing smoking status with records from RERF surveys in 1964-68 (self-reported by subjects when they were alive). Cases and controls who had never married were excluded. Of the female cases exposed to spousal smoking, 16% had squamous or small cell carcinoma, whereas no unexposed cases had those cell types. No information was provided on location of the carcinomas.

The number of female cases exposed to ETS is 73 out of 94 (number exposed/total) compared with 188 out of 270 female controls (crude odds ratio [OR] is 1.52 [95% confidence interval [C.I.] = 0.88, 2.63], by our calculations). Application of logistic regression to the whole study that *includes active smokers*, gives an adjusted odds ratio of 1.5 (90% C.I. = 1.0, 2.5), similar to the crude analysis. It is not stated explicitly that matching variables were included in the logistic regression model. Four additional analyses were conducted on the ETS data alone (i.e., without active smokers). The authors stratified exposure by number of cigarettes smoked per day by husband (0, 1-19, 20-29, 30+) and obtained a marginally significant trend ($p = 0.06$). No dose-response gradient was found in the association between the number of years the husband smoked cigarettes and the risk of lung cancer in female never-smokers; the odds ratio *decreases* from lowest to highest exposure level (2.1, 1.5, and 1.3). Stratified analysis according to recency of exposure to husband's smoking (unexposed, exposed but not within the past 10 years, and exposed within the past 10 years) shows a significant upward trend ($p = 0.05$). Further stratification of exposed subjects by occupation found that lung cancer risk tends to increase across occupational categories in the following order: housewife, white collar worker, blue collar worker. The highest odds ratio occurred for women who had blue collar jobs and were married to men who smoked one or more packs of cigarettes per day, but the number involved was small. It is reported that

additional analyses of the data indicated that factors for matching in the whole study have little influence, but the details are omitted.

Limited histological information is provided. Among cases exposed to spousal smoking, 16% had squamous or small cell cancer, and 84% had adenocarcinoma or large cell cancer. All of the unexposed cases had adenocarcinoma.

The authors conclude that there may be a moderate excess in lung cancer risk associated with passive smoking. The odds ratio for lung cancer among nonsmoking women tends to increase with amount smoked by their husbands, a trend seen among housewives, as well as among women who work outside the home. There was little association with parental smoking or from passive smoking that had ceased more than 10 years previously.

A.4.1.3. *Comments*

The larger study from which the ETS data are taken was primarily intended to investigate the interaction of smoking and ionizing radiation in atomic bomb survivors of Nagasaki and Hiroshima. The information on passive smoking has been collected posthumously in a large percentage of the cases, requiring heavy use of proxy responses. The response rate was not high, however, because some next of kin refused to answer questions about deceased relatives and no attempt was made to locate next of kin of some subjects who had died or moved away from Hiroshima or Nagasaki. The dependence on proxy respondents raises questions about the validity of the exposure data for some measures, particularly in childhood, and about detailed information such as the number of cigarettes smoked per day, duration of smoking habit, and years since cessation of smoking. Information on childhood exposure was obtained for only two-thirds of the subjects. The omission of data on subjects where the next of kin had refused response or the subject had moved may be a source of bias. The diagnosis of lung cancer was not pathologically confirmed in more than 40% of the cases. Also, it is not clear that the subjects are representative of the target population. They had been exposed to ionizing radiation to varying degrees, whatever implication that may have; they are among the survivors, which may suggest selective characteristics; and their age distribution is high, ranging from about 35 to 90 years of age with an average of 70 years or more.

Only ever-marrieds are included in the ETS subjects, which is helpful in the analysis. There is some ambiguity in the statistical analyses, however, in reference to Tables 2 through 6 (the main results). The tables contain odds ratios that are reported to be the result of logistic regression with matching. The details regarding matching in the analysis are not given, but it is reported that analysis of the crude data and matched logistic regression give similar values.

Regarding the analyses for trend, the outcome seems to be sensitive to the measure of exposure used. The odds ratios are strictly increasing for stratification by number of cigarettes smoked per day, but a different pattern emerges when ETS exposure is measured by the number of years the husband smoked cigarettes.

In general, the conclusions are presented more strongly than the data warrant. The assertions are somewhat tenuous that risks tend to increase with amount smoked by the husband, are highest among those who work outside the home and whose husbands are heavy smokers, and decrease with cessation of smoking. Conversely, whereas little association between ETS exposure in childhood and lung cancer is reported, relevant information was available for only two-thirds of the subjects, and its accuracy is questionable because most of that information was provided by proxies. Overall, the observed data suggest that ETS exposure may be related to risk of lung cancer, but there is some potential for misclassification and other sources of bias. Thus, this study provides some useful information on lung cancer risk in passive smokers, but its interpretation needs to be conservative, taking into account the atypical characteristics of the subjects and other concerns described above.

A.4.2. BROW (Tier 3)

A.4.2.1. *Author's Abstract*

"The relation between various risk factors and adenocarcinoma of the lung was evaluated in a case-control study. Subjects were selected from the Colorado Central Cancer Registry from 1979-82 in the Denver metropolitan area. A total of 102 (50 males and 52 females) adenocarcinoma case interviews and 131 (65 males and 66 females) control interviews were completed. The control group consisted of persons with cancers of the colon and bone marrow. The risk estimates associated with cigarette smoking were significantly elevated among males (OR = 4.49) and females (OR = 3.95) and were found to increase significantly ($p < 0.01$) with increasing levels of cigarette smoking for both males and females. For adenocarcinoma in females, the age- and smoking-adjusted odds ratios at different levels of passive smoke exposure followed an increasing overall trend ($p = 0.05$). After additional adjustment for potential confounders, prior cigarette use remained the most significant predictor of risk of adenocarcinoma among males and females. Analysis restricted to nonsmoking females revealed a risk of adenocarcinoma of 1.68 (95% C.I. = 0.39, 2.97) for passive smoke exposure of 4 or more hours per day. Neither sex showed significantly elevated risk for occupational exposures, although males bordered on significance (OR = 2.23, 95% C.I. = 0.97, 5.12). The results suggest the need to develop cell type-specific etiologic hypotheses."

A.4.2.2. *Study Description*

This study was conducted in Denver, Colorado, to evaluate the role of smoking, passive smoking, occupation, community air pollution, and socioeconomic status in the etiology of adenocarcinoma of the lung. Because subjects include active smokers, the data on ETS subjects are part of a larger data set.

Cases and controls were drawn from the Colorado Central Cancer Registry. All subjects were diagnosed with lung adenocarcinoma between 1979 and 1982. Cases are white female Denver residents of at least 6 months' duration. Controls are of similar description to the cases, except that they were diagnosed with colon cancer or bone marrow cancer. Controls were matched on a group basis to produce the same age and gender composition. It is not clear if incident cases were used and whether control sampling was cumulative or density.

The subjects are not matched on smoking status, so the data on ETS subjects alone are unmatched for all variables considered in the larger study. Face-to-face interviews were conducted, blindly, on a total of 149 cases and 169 controls, after attrition in selection and follow-up of 47 cases and 38 controls. The subject was interviewed in 31% of the cases and 61% of the controls; the remaining interviews were conducted with a friend or relative. The mean age of the female cases (controls) was 64.9 (68.2) years; no further details are provided. Clinical verification of lung cancer diagnosis was conducted microscopically.

"Exposed" to ETS is used in two ways, depending on context: (1) the husband smoked (presumably "ever-smoked" is intended, rather than "currently smokes," but that is not explicit); (2) the subject was in the presence of tobacco smoke, from any source, 4 or more hours per day on average. Although there are two operational definitions of exposure, neither includes duration of ETS exposure. Questions were apparently asked regarding exposure in both childhood and adulthood, the latter including sources in the home and in the workplace. No indication was found that the data collected from subjects were checked for internal consistency or against other sources. No mention was found regarding the number of unmarried women in the study or what assumptions may have been made regarding their exposure to ETS when spousal smoking is the source considered (the first of the definitions given above).

The ETS subjects consist of 4 out of 19 (exposed/total) female cases and 7 out of 47 controls, when ETS exposure means the spouse smoked (Definition 1). For exposure from all sources (Definition 2), the corresponding numbers for cases and controls are 4 out of 19 and 6 out of 47, respectively. The crude odds ratio is 1.52 (95% C.I. = 0.39, 5.96) for Definition 1 of ETS exposure and 1.82 (95% C.I. = 0.45, 7.36) for Definition 2 (data communicated from first author, Brownson). A test for trend using hours per day as the exposure measure is conducted on the

whole data set for females *including smokers* (33 of 52 cases are smokers and 19 of 66 controls are smokers; the two exposure categories, 4 to 7 and 8 or more hours per day of exposure to passive smoke, contain a total of only 4 cases and 6 controls who are nonsmokers, but 19 cases and 7 controls who are smokers). The method of Miettenen is applied with stratification on age and smoker status ($p = 0.05$ for trend). The data for never-smokers alone were used in a multiple logistic regression to compare subjects exposed 0 to 3 hours per day with those exposed from all sources 4 or more hours per day (Definition 2 of ETS exposure). Adjustments were made for age, income, and occupation. The reported odds ratio is 1.68 (95% C.I. = 0.39, 2.97). (*Note:* It appears that the upper confidence value may be in error. In view of the outcome for the crude odds ratio, a value about twice what is shown might be anticipated.)

To summarize the statistical tests and authors' conclusions, no significant risk estimates were shown when smoking by the spouse was considered as a dichotomous variable. When the data for both active smokers and passive smokers were stratified according to level of passive smoke exposure, a statistically significant trend in the risk estimates was shown for females ($p = 0.05$) after adjustment for age and cigarette smoking. However, after adjustment by logistic regression for age, income, occupation, and cigarette smoking, with the two exposure categories for ETS combined (> 3 and 4+ hours per day), no significant risk was detected.

A.4.2.3. *Comments*

The study is very small when reduced to the never-smokers alone. The measure of ETS exposure used (hours/day from all sources) is not very specific to differentiate exposed from unexposed persons, particularly exposure 20 to 30 years ago, which may be more relevant than current exposure. Only 15% of the controls have a husband who smoked; only 13% of ETS subjects are exposed from any source 4 or more hours per day. Thus, the cut-point selected by the researchers for general ETS exposure (4+ hours/day) may be too high, resulting in a substantial amount of exposure in the "unexposed" group. For either definition of ETS exposure, however, the percentage exposed is extremely low. Details are lacking also in other areas that may have a bearing (e.g., the treatment of unmarried subjects--whether they were present and, if so, the assumption made regarding ETS exposure).

We experienced some difficulty with the statistical analyses. One of the adjusted procedures is the trend test. Perhaps because the number of ETS subjects is so small, smokers were included in the analysis and then a method was used to attempt to adjust the effects of their presence on the outcome. It would be preferable, in our view, to omit the smokers from the analysis entirely. There are so few ETS subjects in the exposure categories (see above) that it

seems highly unlikely that a test for trend would be significant if based on the ETS subjects alone (we did not have the number of ETS subjects by exposure group, however, so we were unable to conduct the trend test to check the outcome).

When the two exposure categories were combined and only the ETS subjects used, the results were not close to statistically significant (OR is 1.68; 95% C.I. = 0.39, 2.97). We also view that result with caution because using the same data for analysis that were used to determine which variables to adjust for may distort the statistical interpretation. There also may be a typographical error in the upper confidence limit because the value shown is only about half the corresponding value for the crude odds ratio.

The remaining analyses are from the crude odds ratio, 1.52 (95% C.I. = 0.39, 5.99) and 1.82 (95% C.I. = 0.45, 7.36), which suggests a possible association between ETS exposure and lung cancer, although it could easily be ascribed to chance in view of the wide confidence intervals. The study has a very strict requirement for classification as exposed to ETS (4+ hours per day from any source of ETS), which is reflected in only 15% of the controls being designated as exposed (40-60% is more typical). This percentage is only slightly higher than the 12% figure based on simply being married to a smoker. The control subjects thus appear unrepresentative of exposure to the target population, or else the classification of subjects exposed is too rigid. The crude odds ratio may be the preferred statistical measure to represent the outcome of the data, but care should be exercised in using the results from this study in conjunction with those of other studies.

A.4.3. BUFF (Tier 3)

A.4.3.1. *Author's Abstract*

"A population-based case-comparison interview study of lung cancer was conducted from 1979 to 1982 in six Texas coastal counties--Orange, Jefferson, Chambers, Harris, Galveston, and Brazoria--to evaluate the association of lung cancer with occupational and other environmental exposures. Lung cancer mortality rates in these counties consistently have exceeded lung cancer mortality rates observed for Texas and the United States from 1950-69 to 1970-75 for both sexes and races (white and nonwhites).

Histologically and cytologically confirmed incident cases diagnosed during the interval July 1976 to June 1980 among white male and female residents ages 30 to 79 years were ascertained from participating hospitals in the six-county area. Both population-based and decedent comparisons were selected and matched on age, race, sex, region of residence, and vital status at time of ascertainment. The exposures of primary interest in the study of lung cancer are

those associated with occupation (employment in specific industries and occupations) in conjunction with tobacco, alcohol, diet, and residential exposures."

A.4.3.2. *Study Description*

This population-based case-control study was conducted in six coastal counties of eastern Texas to evaluate the association of lung cancer with occupational and other environmental exposures. Those of primary interest are associated with occupation in conjunction with tobacco, alcohol, diet, and residential exposures. The ETS subjects are part of this larger study that includes active smokers.

Cases include males and females ascertained from hospital and State records during 1976-80, except for Harris County, which includes only females from 1977-80. All subjects are white (including Hispanic) county residents of at least 6 months. Cases are incident, without restriction to cell type, and histologically diagnosed to eliminate secondary lung cancers (there is some inconsistency in the article on whether all diagnoses were by histology or whether some were by cytology). Controls were selected from State and Federal records, group matched on age, sex, race or ethnicity, county of residence, and vital status. The candidate sample size is estimated in the report at approximately 1,650, including both sexes, of which just over 700 were lost to attrition in selection or followup for various reasons. Face-to-face interviews were conducted, a large number of which were with next of kin as necessitated by inclusion of decedent cases and controls. For example, for females, the number of subject interviews is only 18% for cases (81/460) and 24% (116/366) for controls. The distribution of ages is similar for cases and controls, based on groupings of 10-year intervals.

"ETS exposed" means having ever lived with a household member who smoked regularly. Exposure sources include the home environment during childhood and adulthood but exclude the workplace. There is no mention of whether data on ETS exposure were cross-checked with other interview questions or other sources. No indication was found regarding unmarried females in the sample and how marital status may affect level of exposure to ETS. Some summary information is provided on the distribution of tumors by cell type, but totals include smokers, so they are not reproduced here. The ETS data for females consist of 33 out of 41 (exposed/total) cases and 164 out of 196 controls; for males, the respective figures are 5 out of 11 and 56 out of 90. For the exposure definition given above, the crude odds ratio reported is 0.78 (95% C.I. = 0.34, 1.81) for females (direct calculation from the data yields a value of 0.81; Buffler apparently added 0.5 to all cells to compensate for inclusion of no subjects in some cells). Little difference was found when female smokers were categorized by number of years lived with a household member who smoked.

No adjusted statistical analysis is provided to account for variables used in matching for the study as a whole, nor is there a test for trend. The authors conclude that no effect of passive smoking is indicated for lung cancer. No attempt is made to evaluate whether exposure to ETS in childhood or adulthood is a factor.

A.4.3.3. ***Comments***

The potential relationship between ETS exposure and lung cancer risk was not a principal issue in the design of this study. As described in the abstract, and more fully in the study description above, other potential etiologic factors were of more central concern. There are several limitations regarding the study's contribution to the epidemiologic evidence on ETS exposure and lung cancer risk. For example, the interview question on exposure to ETS is not very specific. "Having lived with a household member who smoked regularly" does not distinguish between exposure in childhood and in adulthood, between substantial and only light exposure, or between short-term and long-term exposure. One might expect a high percentage of persons to qualify as "exposed" under such a broad definition, and that is what the study demonstrates: 84% of the controls are classified as exposed. With such a high percentage, both cases and controls may include a number of subjects who have experienced very light exposure to ETS. Another concern in this study is the use of decedent subjects. The majority of both male (86%) and female (82%) cases in the study (including smokers) were deceased. Consequently, a very high percentage of interviews was by proxy (82% of cases and 76% of controls).

This study was conducted in a region with a significantly higher age-adjusted mortality rate for lung cancer than for the United States in general. For all ages combined, the overall excess lung cancer mortality in the Texas study area is approximately 30% to 40% and is considerably higher for some age groups, according to the article. This was the apparent motivation for the study, with emphasis on important occupational and industrial exposures for residents of the Texas coastal area, including those associated with shipbuilding and repair, chemical and petrochemical manufacturing, petroleum refining, construction, and metal industries. If these nonsmoking factors affect the incidence of lung cancer, then they may be confounding the attempt to detect an effect from passive smoking. Appropriate statistical methods need to be applied to adjust the effect of each risk factor for the others.

Other factors may affect the ETS analysis also. Harris County, which is frequently addressed in the article as distinct from the other five counties, was apparently added to the study later (case ascertainment began 1 year later there and included only females; 10 of the 11 hospitals that did not participate are in Harris County). Consequently, there are some regional differences

in the study as well as ethnic and racial differences (white and Hispanic). Although the authors took care to match controls on these and other factors, the matching only applies to the whole study (91% and 97% of male and female cases, respectively, are classified as having smoked regularly), not to the ETS subject group specifically, and there is no adjustment for these factors in the analysis. The unadjusted analysis, the insensitive indicator of ETS exposure, and the large use of decedent cases and proxy responses limit the value of this study for assessing any health effects associated with passive smoking.

A.4.4. BUTL(Coh) (Tier 2)

This study was undertaken to explore the role of active and passive smoking in Seventh-Day Adventists in California. Subjects were participants in a larger prospective cohort study of factors affecting health in Adventists.

In 1974, the Adventist Health Study was initiated with the purpose of investigating the associations of a number of lifestyle and nutritional factors with morbidity and mortality in California Seventh-Day Adventists. Registered Adventist households were identified by contacting the clerks of all 437 California Adventist churches. A basic demographic questionnaire sent to all households received a response rate of 58%. In 1976, all subjects aged 25 or older in 1974 were asked to complete a lifestyle questionnaire that included many demographic, medical, psychological, and dietary variables. More than two-thirds of the targeted subjects responded. From the non-Hispanic whites among these respondents, Butler and his colleagues drew two cohorts. One consisted of 22,120 spouses married and living together at the time of completion of the lifestyle questionnaire in 1976 ("spouse-pairs" cohort) and the other of 6,467 individuals participating in an Adventist Health Smog Study of air pollution and pulmonary disease (the "ASHMOG" cohort); about two-thirds of the ASHMOG cohort also was included in the spouse-pairs cohort.

Subjects received annual forms for self-reporting of hospitalizations in the past year. Medical records relating to reported hospitalizations were then reviewed. Mortality was traced in four ways: linkage with California Death Certificate and National Death Index Systems, church clerk notification of deaths entered in church records, and followup of hospitalization history form responses (or nonresponses). Underlying and contributing causes of death were obtained from death certificates. Death certificates were obtained for all reported fatalities.

For the spouse-pairs cohort, subjects were considered unexposed to ETS if their spouses were either never-smokers *or* ex-smokers baptized into the Adventist church--which proscribes tobacco usage--before marriage. Those whose spouses were ex-smokers with less than 5 years of

total smoking also were considered unexposed. All other subjects with ex- and current smoker spouses were classified as exposed.

Incidence rates were calculated using person-years. In the spouse-pairs cohort, age-adjusted lung cancer mortality rates for females married to past or current smokers were higher than those for female spouses of never-smokers, yielding relative risks of 1.94 and 2.47 for past and current smokers, respectively. Comparison of wives with ever- versus never-smoking husbands yielded a relative risk of 2.0. The same age-adjusted relative risk resulted when analyses were restricted to the 9,207 never-smoking females included in the spouse pairs. Virtually identical risk estimates resulted from both Mantel-Haenszel and maximum likelihood analyses. None of the relative risks was statistically significant at the 5% level.

In the ASHMOG cohort, the relative risk of lung cancer adjusted for age and past smoking status among females was 1.16 for women who had lived with a smoker for at least 11 years compared with women who had not lived with a smoker; no difference was observed for women who had lived for less than 11 years with a smoker, although this group was only one-tenth as large as the others. A similar pattern was seen among males who had lived for at least 11 years with a smoker, with an adjusted relative risk of 1.17.

In the spouse-pairs cohort, age-adjusted rates of smoking-related cancers (excluding lung cancer) were only slightly higher among nonsmoking females married to smokers than among nonsmokers (relative risk [RR] = 1.06); the relative risk rose to 1.22 when lung cancers were included.

In the ASHMOG cohort, age-adjusted rates using conditional maximum likelihood analysis for all smoking-related cancers were higher among males who lived with a smoker (RR = 1.45 for 1-10 years; 1.74 for 11+ years) or worked with a smoker (RR = 2.62 for 1-10 years; 1.47 for 11+ years). Among females, in contrast, only one (at RR = 1.03) of the four exposed categories had a higher rate than the nonexposed groups.

All lifestyle questionnaires were administered anonymously, thus reducing the potential for inaccurate responses caused by fear of discovery; respondents to the special supplemental ASHMOG questionnaire were assured of confidentiality but not anonymity.

Although causes of death were obtained from death certificates, review of medical records revealed histological confirmation in 99% of the primary malignancies reported among the spouse-pairs cohort. Thus, substantial misclassification of lung cancer deaths is unlikely. Subsequent study of patients discharged from 1 of the 11 participating Adventist medical centers over a 6-month period indicated that under 2% of study participants failed to report their hospitalizations; serious underascertainment of cases thus also seems unlikely. Losses to followup by study's end totaled only 1.2% of the original study cohort--a very low rate.

Comparing the results of the 1976 questionnaire with those of a supplemental questionnaire given to ASHMOG subjects in 1987, 4.7% of male smokers now reported themselves as "never-smokers" and 1.4% of never-smokers now reported themselves as nonsmokers. Concordance of female responses was even higher. This concordance of responses does not necessarily imply the degree of *accuracy* of responses, only their reliability.

Comparison of responses to the 1987 questionnaire by females revealed that about 6% of those previously classified as not having a smoking spouse now reported having had one; the converse was also true for 6% of the women. These data indicate a mild nondifferential misclassification of exposure, which would push results toward the null.

Information is available on a large number of variables of possible interest as potential confounders or risk mediators. Unfortunately, the modest number of total lung cancer deaths among females in the spouse-pairs cohort (8) or among both sexes in the ASHMOG cohort (13) discourages attempts to control for other potential confounders in addition to age in the analyses. Separate consideration of the association between variables other than passive smoking and age-adjusted lung cancer mortality among women indicated a high relative risk (RR > 4) for spousal blue collar occupation. No other variables produced nearly as strong or consistent an association; in fact, the only other consistent association was a relative risk of 1.3 to 1.6 for nonrural status. Unfortunately, no breakdown of blue collar spousal status by exposure groups was presented.

By virtue of its basic design, the inherent minimization of sources of confounding provided by its study population and the level of information available regarding potential confounders, and other sources of bias, the Butler study has many of the key ingredients to produce convincing results. Unfortunately, this potential goes largely unrealized because of the low number of outcome events occurring during the followup period, which for the most part renders stratification or control for multiple factors simultaneously impractical; even stratification by several age or exposure levels produces unstable results.

Nevertheless, the findings of this study are quite consistent with the hypothesis that ETS exposure of nonsmokers is associated with mildly elevated lung cancer, (active) smoking-related cancer, and ischemic heart disease mortality. Insofar as the study data allow for consideration of potential misclassification and confounding effects, neither misclassification nor confounding can account for the observed association. Because of the limited number of outcome events, several possible confounding factors could not be definitively or adequately addressed in the analyses, and the observed associations were not statistically significant; therefore, the study's findings must be viewed as suggestive but not of themselves convincing.

A.4.5. CHAN (Tier 4)

A.4.5.1. *Author's Abstract*

(*Note*: This study is described in two sources, both of which were used for the description below. Chan et al. [1979] is the more complete description, but it contains considerable attention to active smoking as a cause of lung cancer. Chan and Fung [1982] is a condensed version that specifically addresses nonsmokers. The abstract given here is for the 1979 article. No abstract is provided in the 1982 source.)

"Bronchial cancer is a disease of high and increasing annual incidence in Hong Kong, especially in women, whose age-specific death rates from this cause are among the highest in the world. A case-control study of the relationship of bronchial cancer with smoking was carried out during 1976-77, taking particular note of the histological type of the tumor. Two hundred and eight male and 189 female patients were interviewed, covering about one-half the total number of cases of bronchial cancer registered as dead from the disease in Hong Kong during the period of the survey. The association with smoking was more evident in males than in females, and in squamous and small cell types, as a group, than in adenocarcinoma. Forty-four percent of the women with bronchial cancer were nonsmokers, their predominant tumor being adenocarcinoma, and in them no association could be detected with place of residence or occupation. There was no strong evidence of an association with the use of kerosene or gas for cooking; 23 did not use kerosene. The cause of the cancer in these nonsmoking women remains unknown."

A.4.5.2. *Study Description*

(*Note:* This description is primarily based on Chan et al. [1979]. Chan and Fung [1982] are cited when used as a reference.)

This study is the earliest of four from Hong Kong that consider ETS exposure as a potential etiologic factor for lung cancer incidence in nonsmoking women. Here, however, that objective is secondary to evaluation of the relationship of bronchial cancer with active smoking.

In the whole study, target cases are the lung cancer patients, male and female, in five hospitals in Hong Kong during 1976-77 who were willing and able to be interviewed. Controls are patients of the same general age groups from the orthopedic wards of the same hospitals as the cases. No specific diseases are excluded. Cases are incident and control sampling is density. The candidate sample size is 208 (189) male (female) cases and 204 (189) male (female) controls. Attrition from selection or followup is not reported but appears to be high. Subjects were personally interviewed, when possible. About half of the estimated number of lung cancer cases diagnosed in Hong Kong during the study period were actually interviewed. Some patients were

too ill to answer questions, and more than expected were treated elsewhere than in the hospitals covered. No interviews with next of kin were obtained for the cases interviewed.

The ETS subjects (never-smokers) alone include 84 (2) female (male) cases and 139 (30) female (male) controls. The age distribution of the female cases (controls) is, by percentage, as follows: age less than 40, 7 (5%); ages 40 to 49, 15 (15%); ages 50 to 59, 23 (30%); ages 60 to 69, 23 (22%); and age 70 or more, 32 (28%). Cases with a histological diagnosis were reviewed and verified by reexamination of the pathological specimens. In the absence of a histological specimen, cytological diagnosis was accepted. In some cases, on histological grounds, secondary adenocarcinoma was suspected, and a few cases were rejected after detailed examination of the clinical records. Of the cases, 46 (55%) were diagnosed by histology, 23 (27%) by cytology, and 15 (18%) by radiology and clinical means. Diagnoses by cell type were as follows: squamous or small cell, 19 (22%); adenocarcinoma or large cell, 40 (48%); others and unspecified, 25 (30%). Of the unspecified, 15 had no histological or cytological verification.

ETS subjects are never-smokers. Classification of a subject as exposed or unexposed to ETS is based on the response to these questions: (1) If you do not smoke, have you been exposed to cigarette smoke from other people at home or at work? (2) Does your husband/wife smoke? (If "yes," how many cigarettes per day?) (The first question is included in Chan et al. [1979]. The second one is from a personal communication of Linda C. Koo.) No information is reported on the distribution of tumors by central and peripheral location.

The ETS data on females based on question 1, above, consists of 50 out of 84 (unexposed/total) cases and 73 out of 139 controls. The authors state that "this is a rather subjective approach to the problem." No statistical estimates are provided; our calculation of the crude odds ratio is 0.75 (95% C.I. = 0.43, 1.30). No clear conclusion is drawn regarding the potential relationship between ETS exposure and lung cancer occurrence, but the authors imply that no connection was found (which the odds ratio and confidence interval amply support). The authors found no particular occupation as being dangerous. Their findings also do not support air pollution as a factor, and they provide no strong evidence that cooking with various types of fuel is relevant.

A.4.5.3. *Comments*

Although data on spousal smoking were collected along with an indication of the number of cigarettes smoked per day, they are referred to only in the 1982 article, where the authors note without further elaboration that more nonsmoking cases have nonsmoking spouses. It is reported that answers to the question, "Are you exposed to the tobacco smoke of others at home or at

work?" gave no indication that other people's smoking was a risk factor for lung cancer in nonsmokers, with 40.5% of cases and 47.5% of controls answering yes to this question. Why the data for spousal smoking are not given and analyzed is unknown. The question about general ETS exposure combines sources in the household and workplace and refers only to current exposure without a measure of duration, which would likely affect any risk associated with passive smoking.

Although it is reported that cases and controls are similar in age, occupation, and other characteristics, comparability is questionable. The article cites a criticism of the whole study (including smokers) for use of orthopedic patients as controls, on the basis that some patients may be hospitalized with smoking-related diseases (e.g., osteoporosis). It was found that the controls smoke more than a group representative of the population of Hong Kong. This would create a bias toward negative association. Although these comments refer to smoking habits, they suggest the potential for selection bias of controls that may extend to nonsmoking controls as well.

It is noted, also, that there are more cases from Hong Kong Island than would be expected from the population distribution of Hong Kong as a whole, possibly due to more success contacting cases in Hong Kong Island than in Kowloon. The authors caution about reaching any conclusion about the distribution of cases within Hong Kong as a whole. The failure to follow up on patients who were eventually treated at other hospitals or were too ill to be interviewed is itself, of course, a potential source of bias.

Other differences are apparent between cases and controls. Among nonsmokers, a higher percentage of cases than controls (1) are Cantonese (81 vs. 70) or (2) have ever cooked with kerosene (73 vs. 60). It is speculated that the Cantonese diet, high in nitrite or nitrate content, may be a factor in lung cancer incidence (Chan and Fung, 1982). More broadly, these comparisons between cases and controls indicate differences in ethnic composition, lifestyle, and socioeconomic status that are difficult to assess.

In summary, ETS subjects are not matched in the design, and an adjusted statistical analysis is not conducted. Consequently, potential sources of bias are not controlled. There is substantial basis to question the comparability of cases and controls, as described above. Data quality is suspect because confirmation of primary lung cancer was limited and cases were missed because patients were too ill to be interviewed personally or were eventually treated at another hospital. Also, the question posed to subjects for classification as exposed or unexposed to ETS is sufficiently general to invite a subjective response. Overall, methodological shortcomings hamper the interpretation of this study's results.

The finding that spousal smoking appears to be more frequent in controls, mentioned in the 1982 report, is noted to be at variance with the Hirayama study, which may have motivated

the authors to conduct this secondary analysis of ETS exposure using their previously collected data. Whatever the motivation, the limitations of the original study, which was not designed to assess passive smoking, limit this study's value for assessing ETS exposure and lung cancer.

A.4.6. CORR (Tier 2)

A.4.6.1. *Author's Abstract*

"Questions about the smoking habits of parents and spouses were asked in a case-control study involving 1,338 lung cancer patients and 1,393 comparison subjects in Louisiana, United States. Nonsmokers married to heavy smokers had an increased risk of lung cancer, and so did subjects whose mothers smoked. There was no association between lung cancer risk and paternal smoking. The association with maternal smoking was found only in smokers and persisted after controlling for variables indicative of active smoking. It is not clear whether the results reflect a biological effect associated with maternal smoking or the inability to control adequately for confounding factors related to active smoking. This preliminary finding deserves further investigation."

A.4.6.2. *Study Description*

This study was conducted in Louisiana to investigate the relationship of smoking habits of parents and spouses to lung cancer occurrence. Results of the study were published in 1983; some clarifying details regarding study methodology were supplied in a 1984 paper addressing only the effects of active smoking. The accrual period is not stated; cases are probably a mixture of prevalence and incidence, and controls are cumulatively sampled. ETS subjects constitute a small portion of the whole study, which includes active smokers.

Cases consist of patients diagnosed with primary lung cancer, exclusive of bronchioalveolar carcinoma, from participating hospitals in several Louisiana parishes (counties), predominantly in the southern part of the state. A total of 302 female and 1,036 male cases and an equal number of controls are included in the whole study. Controls were selected from other patients, excluding those diagnosed with emphysema, chronic bronchitis or obstructive pulmonary diseases, or certain cancers (laryngeal, esophageal, oral cavity, and bladder). They were matched to cases on hospital, age (± 5 years), sex, and race. Information about active and passive smoking was obtained by interview (presumably face-to-face and unblinded), with responses obtained from next of kin in 24% of cases and 11% of controls; no information on refusals is provided. ETS subjects were identified by exclusion of individuals who had ever smoked or had never been married, which eliminated 279 female and 1,026 male cases. Removal of subjects with no spousal

smoking data eliminated one additional female and two male cases, leaving 22 female and 8 male cases. Similarly, a total of 1,080 men and women were excluded from controls. No demographic comparisons are given, either for the whole study or for the ETS subjects alone, nor is the number of proxy responses provided for the ETS subjects. Histological confirmation was obtained for 97% of cases in the whole study, including ever-smokers.

"ETS exposed" is used in two ways, depending on the analysis given: (1) the spouse has smoked at least 1 pack-year of cigarettes or (2) the spouse currently smokes. Units of exposure are pack-years and current consumption is in cigarettes per day for (1) and (2), respectively. ETS exposure in childhood means that at least one parent smoked during most of the subject's childhood. Types of tobacco smoking other than cigarettes (e.g., cigars and pipes) are referenced indirectly in regard to interview questions but are not included in the data analysis. Other sources of exposure, either at home or in the workplace, are not considered. Never-married women are excluded from ETS analysis, but no information is given on the number of nonsmoking widows and divorcees and how they were handled with regard to ETS exposure. Adenocarcinoma accounts for 54% of lung cancers in nonsmoking women, compared with 22% in women who actively smoke. No further histological breakdowns are provided.

For the main analysis of spousal smoking, exposure constitutes 1 or more pack-years of spousal cigarette consumption. ETS-exposed subjects include 14 (61) of 22 (133) female cases (controls) and 2 (26) of 8 (180) male cases (controls). These data yield a crude odds ratio of 2.07 (95% C.I. = 0.81, 5.25) for females (confidence interval was calculated by reviewers). Among females, stratification by 0, 1 to 40, and 41 or more pack-years of exposure yields odds ratios of 1.0, 1.18, and 3.52, respectively, with the highest exposure category being statistically significant at $p < 0.05$. No adjusted results are presented. It is, however, reported that analyses based on current daily spousal cigarette consumption produced very similar results to the pack-year analyses. In addition, it is reported that neither exclusion of proxy interview data nor restriction to same-race subjects significantly alters the results. Analysis of parental smoking during childhood embraces the combined population of smokers and nonsmokers, adjusting for smoking status by logistic regression. Maternal smoking is associated with significantly increased estimated risk of lung cancer (OR = 1.38, $p < 0.05$) but paternal smoking is not (OR = 0.83). No association was noted among nonsmokers alone, but the authors note that small numbers preclude adequate analysis of this group.

A.4.6.3. *Comments*

The study entails a major multicentric effort to assemble hospital-, age-, race-, and sex-matched lung cancer cases and controls from Louisiana hospitals. Its use of trained local interviewers familiar with the region's culture increases the probability of obtaining accurate interview data for the nearly 3,000 subjects involved. Exclusion of active smokers to assess ETS exposure, however, exacts a toll on the study's power and validity. Because the initial matching of cases and controls did not include smoking status, the ETS subjects are unmatched in the analyses of spousal and parental smoking. This potential problem is not addressed by the authors. The lack of any demographic information on cases and controls leaves the comparability of these groups uncertain.

The potential problem of misdiagnosis of primary lung cancer is minimized by the high rate (97%) of histological case confirmations. Eligibility criteria for controls were intended to exclude smoking-related diseases. Some 15% of the controls had cardiovascular disease, however, which has been associated with both active and passive smoking. The authors also speculate that the inclusion of adenocarcinoma, reportedly less smoking-associated than other lung cancers, may have diluted the significance of their results, but they do not present analyses using their extensive histological data to assess this question.

Restriction of the spousal smoking analysis to ever-married individuals eliminates potential bias due to differences between lifelong single and married individuals. Stratification by gender controls for any sex-related differences. Both race and proxy interviews were reported to have no effect on the spousal smoking results, and the spousal smoking association was still observed after division of women into more than and less than 60 years of age. A small number of nonsmoking ever-married cases (8 males and 22 females for this study) hampers efforts to control statistically for other factors; nonetheless, direct adjustment for age and race is needed.

It is concluded that females married to heavy smokers have an increased risk of lung cancer. A significant increase in risk for nonsmokers was found from maternal but not from paternal smoking in childhood. The results for childhood exposure, however, use statistical methods to adjust for the presence of active smokers. It would be preferable, in our view, to remove the data for active smokers prior to analysis. The potential for bias in all of the analyses, which could be in either direction and may or may not be of consequence, needs to be kept in mind when using this study's results.

A.4.7. FONT (Tier 1)

A.4.7.1. *Author's Abstract*

"The association between exposure to ETS and lung cancer in female lifetime never-smokers was evaluated using data collected during the first 3 years of an ongoing case-control study. This large, multicenter, population-based study was designed to minimize some of the methodological problems that have been of concern in previous studies of ETS and lung cancer. Both a cancer control group and a population control group were selected in order to evaluate recall bias. A uniform histopathologic review of diagnostic material was conducted for case confirmation and detailed classification. Biochemical determination of current exposure to tobacco and screening of multiple sources of information to determine lifetime nonuse were employed to minimize misclassification of smokers as nonsmokers.

A 30% increased risk of lung cancer was associated with exposure to ETS from spouse, and a 50% increase was observed for adenocarcinoma of the lung. A statistically significant positive trend in risk was observed as pack-years of exposure from spouse increased, reaching a relative risk of 1.7 for pulmonary adenocarcinoma with exposures of 80 or more pack-years. The predominant cell type of the reviewed, eligible lung cancer cases was adenocarcinoma (78%). Results were very similar when cases were compared with each control group and when separate analyses were conducted for surrogate and personal respondents. Other adult-life exposures in household, occupational, and social settings each were associated with a 40% to 60% increased risk of adenocarcinoma of the lung. No association was found between risk of any type of lung cancer and childhood exposures from father, mother, or other household members."

A.4.7.2. *Study Description*

This study was initiated in 1985 in five major U.S. metropolitan areas to investigate the association between exposure to ETS and lung cancer in female lifetime never-smokers. The study was designed specifically to address this issue and includes only never-smokers. The results reviewed are from an interim report, with the completed study expected to encompass an additional 2 years of case accrual.

Patients were English-, Spanish-, or Chinese-speaking female residents 20 to 79 years of age who have never used tobacco, have no prior history of malignancy, and have histopathologically confirmed primary lung cancer. The lung cancers were originally diagnosed at participating hospitals in Atlanta, Houston, Los Angeles, New Orleans, and the San Francisco Bay area, between December 1, 1985, and December 31, 1988. Two control groups were assembled, one from colon cancer patients and the other from the general population, with the same general

eligibility requirements as cases. The population control group, consisting of women selected from the general population by random digit dialing and by sampling from Health Care Financing Administration files, was frequency-matched on age (< 50, 50-59, 60-69, 70+), with two controls per case. The colon cancer controls were frequency-matched to cases by 10-year age groups and by race. The lung cancer group consists of incident cases, but there is no indication whether density or cumulative sampling was employed for either control group. Exposure data were collected in face-to-face, apparently unblinded, interviews.

Extensive efforts were made to include only never-smokers. For cases and colon cancer controls, medical records were reviewed for tobacco use and physicians were contacted as necessary. Eligible cases not previously excluded and all population controls were contacted by telephone to screen for prior use of tobacco (no more than 100 cigarettes smoked or use of any tobacco in any form for more than 6 months). Urinary cotinine was bioassayed to eliminate any misreported current smokers.

A total of 514 eligible cases were identified, of which 83 were not interviewed for unspecified reasons and 2 had urinary cotinine levels consistent with active smoking. Independent histopathologic review by a pulmonary pathologist was performed for 84% (359/429) of the lung cancer cases, resulting in nine exclusions. Only the remaining 420 cases are included in the study. Colon cancers were not reviewed. Of 489 (1,105) eligible colon cancer (population) controls, 131 (311) were not interviewed and 7 (14) were excluded for high urinary cotinine. Proxies were interviewed for 143 (34%) of the lung cancer cases and 35 (10%) of the colon cancer controls, whereas no proxies were used for the population controls.

Cases and the two control groups all have similar age distributions, with the majority of subjects between 60 and 79 (73%, 74%, and 74% of the cases, colon, and population groups, respectively). The proportion of whites is similar across all groups (63-69%), but the control groups contain a somewhat higher proportion of blacks and lower proportion of other minorities, and a little higher percentage of high school graduates (76% and 79% vs. 68%). Cases and controls are comparable by metropolitan size of adulthood and childhood residences and also by annual income.

Four sources of adult ETS exposure are assessed: smoking by (1) spouse(s) and (2) other household members while living with the subject, and reported exposure to ETS in (3) occupational and (4) social settings. Three sources of possible exposure in childhood (up to 18 years of age) are considered: smoking by (1) father, (2) mother, or (3) other household member(s) while living in the subject's home for at least 6 months. Subjects are characterized as ever- versus never-exposed with a subanalysis by tobacco type (cigarette, pipe, or cigar). Years of exposure are also tabulated. In addition, cigarettes per day for spouse and for other household sources and

pack-years for spouse(s) are calculated. No checks on exposure (aside from the cotinine screening) are reported.

Adenocarcinoma is the dominant type of lung cancer among study subjects, representing 76% (311/409) of all cases included in the study (with the exception of 11 cases with "review pending") and also 78% (281/359) of all independently confirmed primary bronchogenic carcinomas among those cases. Other cell types include 12% (48/409) large cell, 7% (27/409) squamous cell, 3% (14/409) small cell, and 2% (9/409) other cancers. No data on airway proximity are provided.

The final study population (for this interim report) consists of 420 lung cancer cases, 351 colon cancer controls, and 780 population controls. Exposure to spousal smoking from all types of tobacco is reported for 294 cases, 231 colon cancer controls, and 492 population controls, yielding similar odds ratios (adjusted for age, race, area, income, and education) of 1.28 (95% C.I. = 0.93, 1.75) and 1.29 (0.99, 1.69) using the respective control groups. Elevated but statistically nonsignificant observed risks are also observed when cigarette, cigar, and pipe exposure are assessed separately, with either control group. Restriction of analyses to the 281 independently reviewed adenocarcinomas results in stronger associations, with adjusted odds ratios of 1.44 (95% C.I. = 1.01, 2.05) and 1.47 (1.08, 2.01) for all types of tobacco, and increased odds ratios for each type of tobacco as well.

Odds ratios were also calculated for ETS exposure from cigarette smoking alone, with the two control groups combined (the individual results using each control group are entirely consistent). For all lung cancer types combined, the adjusted odds ratios are 1.21 (0.96, 1.54) for spousal smoking, 1.23 (0.97, 1.56) for other household members, 1.34 (1.03, 1.73) for occupational environments, and 1.58 (1.22, 2.04) for social exposure, the last two of which are significant ($p < 0.05$ and 0.01, respectively). The corresponding odds ratios for adenocarcinoma cases alone continue to be uniformly higher: 1.38 (95% C.I. = 1.04, 1.82), 1.39 (1.05, 1.82), 1.44 (1.06, 1.97), and 1.60 (1.19, 2.14). The odds ratio tends to increase over years of exposure for all carcinomas combined and for adenocarcinoma alone, although not monotonically (without downturns). The tests for upward trend are all significant or suggestive, with p-values ranging from < 0.001 to 0.07 (these p-values are one-half those reported, which apply to a trend in either direction). Finally, for spousal smoking measured in pack-years, the upward trend is significant for adenocarcinoma alone and for all lung cancers together ($p < 0.005$ and 0.04, respectively).

The authors interpret their findings as evidence of a causal relationship between ETS exposure in adulthood and lung cancer in never-smoking women. In contrast to adulthood, ETS exposure during childhood shows no association with lung cancer, for either all cell types

combined or adenocarcinoma alone. Adjusted odds ratios for childhood exposure tend to be slightly (but not significantly) below unity for all exposure sources.

A.4.7.3. *Comments*

This study is much larger than any other ETS case-control study. More than 400 never-smoking female lung cancer cases were enrolled in just over 3 years, in contrast to the 25 to 75 cases typical of most studies, and two control groups were formed, totaling more than 1,200 subjects. Additionally, the cases and controls are drawn from five widely dispersed metropolitan centers in the United States, representing a population of approximately 18.5 million people, about 8% of the U.S. population. This characteristic increases the generalizability of the study and diminishes the potential for bias related to locale.

Extensive efforts were made to achieve precision and validity, in evidence throughout the study. Cases and controls are highly comparable. They are frequency-matched on age and, for colon cancer controls, on race as well. The distributions of other demographic variables--annual income, childhood residence, and adult residence--are quite similar between cases and both control groups. The control groups contain a little higher (lower) proportion of blacks (Asians and Hispanics) and a higher percentage of high school graduates. These differences, however, should not have influenced the reported associations because all odds ratios are adjusted for race and education.

The use of incident cases reduces the potential for selection bias, and the implementation of two control groups allowed for assessment of potential bias from comparison with cancer patients or the general population alone. The similarity of results obtained from the two control groups suggests little bias from choice of controls.

The use of a multistep procedure to eliminate inclusion of former or current smokers reduces the potential for smoker misclassification as a source of upward bias. As a further safeguard, urinary cotinine was bioassayed for all consenting persons to exclude those likely to be current smokers. This is the only published study we are aware of to implement this precaution. Attention to histopathology is also very thorough. Inclusion of only histologically diagnosed primary carcinoma reduces the likelihood of diagnostic error, which is further reduced by the use of independent histopathologic review of most cases by a single pulmonary pathologist. The study's histopathologic findings bring out two interesting points. First, comparison of cell type diagnoses between hospital and independent reviewers revealed poor concordance for large (56%) and squamous (67%) cell carcinomas, indicating that cell-type-specific analyses for these cancers may be misleading, particularly if all diagnoses are not made by the same pathologist. The

histopathologic review also resulted in a net increase of adenocarcinomas from 244 to 281, 78% of the total, a higher proportion than in most but not all other studies. The statistical results were stronger when limited to cases of adenocarcinoma alone.

Exposure information was obtained in the most reliable way, by face-to-face interviews with each interviewer trained and fluent in the subject's primary language. Information for a substantial proportion of lung cancer cases (34%) was obtained from proxy respondents, but fewer proxies were required for colon cancer controls (10%), and none were used for population controls. The use of proxy respondents raises the possibility of information bias, but their exclusion reportedly did not alter the study's findings. The apparent lack of blinding also raises the possibility of interviewer bias, but it is unlikely that such bias (or recall bias, for that matter) would focus its effect on adenocarcinoma. Also, the same relationships hold whether the colon cancer or population controls are used.

Particular attention is paid to all sources of ETS exposure, which is more informative than addressing only spousal smoking, with four sources in adulthood and three in childhood evaluated both individually and in combination. Additionally, subjects are counted as exposed to the ETS of a spouse or other household smoker only while living with the source, giving a more accurate account of exposure than simply determining whether a spouse or household member ever smoked. Consequently, the measures of ETS exposure are more specific by source, and probably more accurate, than in most studies. This reduces bias toward unity in the odds ratio arising from poor distinction between exposed and unexposed subjects. Still, further accuracy might have been achieved by stipulating that smoking must occur in the subject's household or presence, but this is a minor point.

Most of the standard risk modifiers, such as age, race, geographic area, income, and education, are adjusted for in all analyses and thus can be ruled out as sources of the observed results. Although information on diet, occupational exposures, and "other exposures of interest" were collected, these factors are not addressed in this interim report. Thorough treatment of the possible impact of these factors presumably will be undertaken after subject accrual is finished and published in the completed study.

To summarize, this study was designed specifically and solely to address the topic of ETS as a potential lung cancer risk to nonsmoking women. Several issues were given special attention, such as the potential misclassification of smoking status, histopathologic specificity, recall bias, and source of ETS exposure. Histopathologic specificity has not been convincingly demonstrated in prior studies, and the meaning of "exposed to ETS" has differed widely between studies, even those addressing spousal smoking only. The remaining issues are largely related to controlling potential sources of bias and confounding to enhance validity. The qualitative rigor and

completeness of detail in this study is impressive. In addition, it is quite large, which increases precision of estimates and power to detect an association, if it exists. Use of dietary, occupational, and other exposure data in the analyses, along with an additional 2 years of subject accrual, will make the completed study for which this constitutes an interim report even more valuable. As it stands, however, this study is already the largest and most useful case-control study available. Its high quality and the reasonable consistency of the evidence across sources of ETS exposure strongly support an increase in lung cancer incidence associated with passive smoking.

A.4.8. GAO (Tier 3)

A.4.8.1. *Author's Abstract*

"A case-control study involving interviews with 672 female lung cancer patients and 735 population-based controls was conducted to investigate the high rates of lung cancer, notably adenocarcinoma, among women in Shanghai. Cigarette smoking was a strong risk factor, but accounted for only about one-fourth of all newly diagnosed cases of lung cancer. Most patients, particularly with adenocarcinoma, were lifelong nonsmokers. The risks of lung cancer were higher among women reporting tuberculosis and other preexisting lung diseases. Hormonal factors were suggested by an increased risk associated with late menopause and by a gradient in the risk of adenocarcinoma with decreasing menstrual cycle length, with a threefold excess among women who had shorter cycles. Perhaps most intriguing were associations found between lung cancer and measures of exposure to cooking oil vapors. Risks increased with the number of meals cooked by either stir frying, deep frying, or boiling; with the frequency of smokiness during cooking; and with the frequency of eye irritation during cooking. Use of rapeseed oil, whose volatiles following high-temperature cooking may be mutagenic, was also reported more often by the cancer patients. The findings thus confirm that factors other than smoking are responsible for the high risk of lung cancer among Chinese women and provide clues for further research, including the assessment of cooking practices."

A.4.8.2. *Study Description*

This study was undertaken in Shanghai, China, during 1984-86 to explore reasons for the high rates of lung cancer among women in Shanghai. Potential etiologic factors associated with the high occurrence of adenocarcinoma among females in a population where few women smoke cigarettes is of particular interest. Several potential risk factors, in addition to exposure to ETS,

are investigated. These are included in the abstract above. Smokers are included in the study as well as nonsmokers.

A special reporting system for lung cancer linked with the area's medical facilities was set up for the study period, integrated with the Shanghai Cancer Registry. Incident cases of lung cancer occurring among 35- to 69-year-old female residents of urban Shanghai from February 1984 to February 1986 were interviewed by trained study personnel. Controls were women selected from residents of the urban Shanghai community by stratified random sampling designed to mimic the age distribution of Registry-reported lung cancer cases during 1980-81. It is not clear whether cumulative or density sampling was employed.

Face-to-face interviews were conducted with 672 cases and 735 controls. No cases refused to be interviewed, but 93 died before interview and were therefore excluded; it is not mentioned whether there were any refusals among potential controls. Nonsmokers composed 436 of the cases and 605 of the controls. In the total subject population, distribution of age, education, and marital status between cases and controls is described as similar, except for a larger proportion of controls (32% vs. 20%) in the oldest age group (65-69 years). The age distribution in the ETS population alone is not described.

ETS exposure is based on living with a smoker. For general exposure in childhood or adulthood, exposed subjects are those who ever lived with a smoker. For spousal smoking alone, however, women are ETS exposed only if they lived with a smoking husband for at least 20 years. General ETS exposure sources include all household members but not coworkers. Verification of exposure data was not mentioned. Based on the reported exposure criteria, widows and divorcees would have been included in the spousal smoking data set, whereas never-married women would have been excluded.

For ETS subjects, 246 (375) cases (controls) from the total of 672 (735) cases (controls) are included in Table II of the article that lists the number of cases and controls by number of years lived with a smoking husband. Presumably, the 190 cases and 230 controls not included in the table are unmarried (or never-married) and do not include women married and living with a nonsmoker; no explanation is provided in the article.

Among nonsmoking women included in Table II, 189 out of 246 cases and 276 out of 375 controls had lived with a smoking husband for at least 20 years. These subjects were divided into exposure categories of 20 to 29, 30 to 39, and 40 or more years for comparison with the "unexposed" (< 20 years spousal smoking) subjects. The authors present no unadjusted analyses, but calculations from their raw data yield an overall odds ratio of 1.2 and stratum-specific odds ratios of 1.2, 1.3, and 1.1 for 20 to 29, 30 to 39, and 40 or more years of exposure, respectively. Age- and education-adjusted odds ratios increase with the number of years exposed: 1.1 (95%

C.I. = 0.7, 1.8) for 20 to 29 years, 1.3 (0.8, 2.1) for 30 to 39 years, and 1.7 (1.0, 2.9) for 40 or more years. The authors report an odds ratio of 2.9 (1.0, 8.9) for squamous and oat cell cancer for 40 years of exposure or less but present no other type-specific results.

Information on cell type is available for the 542 (81%) study cases diagnosed by histology or cytology; the rest of the cases were diagnosed by radiological or other means. Diagnostic evidence was reviewed by a team of pathologists and clinicians. For the lung cancer cases histologically typed, adenocarcinoma (61%) greatly predominates, followed by squamous (22%), small cell (6%), and other (11%) types. No breakdowns of tumor type are provided for the ETS group.

The authors conclude that ETS may account for some, but probably few, of the cancers among nonsmokers, because there was little or no association with ever having lived with a smoker. Among nonsmoking women married to smokers, however, there was an upward trend in risk associated with increasing years of exposure. This latter finding is consistent with reports in other parts of the world. Little evidence was found to implicate the type of fuels used for cooking in lung cancer risk; occupational factors did not appear to be important, nor did familial tendency to lung cancer. Our data suggest, however, that prior lung diseases, hormonal factors, and cooking practices may be involved. Most provocative is the association with cooking oil volatiles, and further investigations are needed to evaluate their contribution to the high lung cancer rates among Chinese women in various parts of the world.

A.4.8.3. *Comments*

The number of ETS subjects for analysis is relatively large. Unfortunately, the study is unmatched, with no demographic breakdown of the cases and controls, either for the whole study or for the ETS subjects alone. Controls were selected to make their age distribution similar to that expected for cases in the whole study, but the similarity may not apply to ETS subjects alone. Consequently, there is little basis for evaluating the comparability of cases and controls. Age and education were adjusted for in the analyses, which has some compensatory value.

The use of direct interview with all subjects without reliance on proxies to gather exposure information should enhance the validity of the exposure comparisons. On the other hand, the possible use of unblinded interviewers could have biased results. In light of the lack of association noted for passive smoke exposure as a child or adult, however, it is unlikely that such a bias produced the observed association between spousal smoking and lung cancer. For evaluation of spousal smoking, the reference group can hardly be classified as "unexposed" to spousal smoking because it includes women who lived with a smoking husband for up to 20 years. The

investigators probably selected the cutoff level of exposure for their spousal smoking reference group to balance the numbers in each exposure category, as a practical matter. The reference group contains an undisclosed number of women who may have been exposed to spousal smoking for many years, potentially creating a substantial bias toward the null hypothesis (no association between ETS exposure and lung cancer). Consequently, the odds ratios may be biased downwards. The relative comparison across years of spousal smoking, however, is not affected. An increasing trend in the odds ratio was observed, but no statistical test for trend is cited. In a similar vein, it appears that active smokers *may* have been included in the data analysis of overall ETS exposure. That factor, in combination with the use of ever- versus never-exposed classifications without regard to degree or duration of ETS exposure in the analyses, may have reduced the likelihood of detecting any positive association that may exist.

The study appears to have focused on potential risk factors other than ETS. Unfortunately, the effects of these other factors on the ETS results were not explored, even though many of these appeared to be stronger risk factors than passive smoking. Some factors, such as age and education, *were* adjusted for in all analyses. Control for education should in turn produce a degree of adjustment for factors related to socioeconomic status (e.g., dwelling size and quality of diet).

Overall, the study presents evidence of a mild duration-dependent association between lung cancer and spousal smoking that skirts statistical significance. Several sources of misclassification bias are possible, but most would tend to bias the odds ratio downward. The study was not, however, specifically designed to evaluate the ETS-lung cancer hypothesis. Information was collected and analyzed on a number of other potential risk factors, but they were not adjusted for in the analysis. Coupled with other limitations, this omission reduces the weight of the study's results with regard to ETS, although they support an increase in lung cancer risk with spousal smoking.

A.4.9. GARF (Case-Control) (Tier 2)

A.4.9.1. *Author's Abstract*

"In a case-control study in four hospitals from 1971 to 1981, 134 cases of lung cancer and 402 cases of colon-rectum cancer (the controls) were identified in nonsmoking women. All cases and controls were confirmed by histologic review of slides, and nonsmoking status and exposures were verified by interview. Odds ratios increased with increasing number of cigarettes smoked by the husband, particularly for cigarettes smoked at home. The odds ratio for women whose husbands smoked 20 or more cigarettes at home was 2.11 (95% C.I. = 1.13, 3.95). A logistic

regression analysis showed a significant positive trend of increasing risk with increasing exposure to the husband's smoking at home, controlled for age, hospital, socioeconomic class, and year of diagnosis. Comparison of women classified by number of hours exposed a day to smoke in the last five years and in the last 25 years showed no increase in risk of lung cancer."

A.4.9.2. *Study Description*

This study was undertaken in New Jersey and Ohio to investigate the relationship of involuntary smoking to primary lung cancer. All data were collected specifically for this study, and only nonsmokers were included as subjects. Cases are the lifelong nonsmoking women histologically diagnosed with primary lung cancer during 1971-81 in four participating New Jersey and Ohio hospitals. Controls selected from patients with colorectal cancer were matched 3 to 1 to a case on hospital and age (± 5 years). Subjects were not restricted to incident cases, and controls were apparently cumulatively sampled. Exposure data were obtained by blinded, face-to-face interviews with subjects or their relatives.

A total of 1,175 female lung cancer cases were initially identified from medical records. Exclusion of women found to be current or former smokers or not to have histologically verified primary lung cancer eliminated 1,041 of the identified cases, leaving 134 ETS subjects. Interviews were conducted with patient, spouse, or child in about 75% of the subject population, whereas the rest were conducted with another relative. The age distributions of cases and controls are nearly identical.

ETS exposure includes pipe and cigar use as well as cigarette smoking. Three sources of passive smoking are considered, which will be referred to as follows: "exposure to husband's smoke" means having a husband or other related cohabitant who smokes more than occasionally, either (1) anyplace or (2) at home; "general exposure" applies to the smoke of others at home, work, or otherwise who have smoked more than occasionally during the past (1) 5 years or (2) 25 years; and "childhood exposure" refers to experiencing ETS from any source during childhood. Husband's smoking is quantified as cigarettes per day and years smoked; general exposure is given as average hours per day; and childhood exposure is treated as a dichotomous variable. Only 57 percent of the cases were women living with a husband at the time of diagnosis. No checks on exposure status are described, and no classification of subjects by marital status was implemented. Adenocarcinoma (87) predominates among lung cancer cases, followed by large cell (21), small cell and miscellaneous (15), and squamous cell cancer (11); no data on airway proximity are provided.

Ninety of 134 cases were exposed to husband's (or other relative's) smoking at home, compared with 245 of 402 controls, giving a crude odds ratio of 1.31 (reported 95% C.I. = 0.99,

1.73; C.I. calculated by reviewers is 0.87, 1.98). For husband's smoking of 20 or more cigarettes per day, the highest exposure category, the odds ratio increases to 2.11 (1.13, 3.95). Husband's smoking averaged 11.5 cigarettes per day for the exposed subject. For husband's smoking anyplace, 91 of 134 cases and 254 of 402 controls were exposed, giving a crude odds ratio of 1.23 (0.94, 1.60). At the highest exposure category, 40 or more cigarettes per day, the odds ratio is 1.99 (1.13, 3.50). Cigar and pipe smoking alone yields odds ratios of 1.17 and 1.13 for husband's smoking at home and anyplace, respectively. There are statistically significant trends for both husband's smoking at home and for smoking anyplace when measured by cigarettes per day, but not when evaluated by number of years smoked. The odds ratio for ETS exposure from husband's smoke, both total and at home, is calculated by source of interview respondent for the categories of "self," "husband," "daughter or son," and "other." It is readily apparent that the excess risk is attributable to "daughter or son," with some contribution from "other." *None* of the excess risk is attributable to "self" or "husband."

General smoke exposure also shows an association with lung cancer. Exposure over the past 5 and past 25 years yields odds ratios of 1.28 (0.96, 1.70) and 1.13 (0.60, 2.14), respectively. The odds ratios do not increase with increasing level of exposure, however, and none of the associations is statistically significant. No association was found between childhood smoke exposure and lung cancer (OR = 0.9, 0.74-1.12). When the odds ratio is calculated by source of respondent, "other" and "self" account for the excess risk when smoking for 5 years is the measure; for 25 years of smoking, "other" and "daughter or son" account for the excess risk.

Stratification by cell type reveals that husband's smoking is much more strongly associated with squamous cell (OR = 5.00, both for smoking at home and anyplace) than adenocarcinoma (corresponding ORs = 1.33 and 1.48); no association with other cell types was detected. Stratification by age and socioeconomic status suggests little effect of these variables on the results. The results, however, appear to be sensitive to whether the interview data were obtained from the subject or a surrogate (offspring, relative, etc.), as noted above.

A logistic regression analysis including adjustment for age, hospital, socioeconomic status, and year of diagnosis was undertaken for passive smoking. Cigarettes per day of husband's at-home smoking is significantly associated with lung cancer, with an estimated relative risk of 1.7 at exposure of 20 cigarettes per day compared to none. In contrast, husband's smoking outside the home is *not* significantly associated with lung cancer, although the estimated relative risk is 1.26 for 20 cigarettes per day. General smoke exposure is not significantly associated with lung cancer, for either the past 5 years or 25 years of exposure. Adjustment for type of respondent reportedly had no significant effect on the logistic regression results.

A.4.9.3. *Comments*

The abundance of nonsmoking cases (134) and controls (402) in this study relative to most ETS studies gives it above-average statistical power. Comparability of cases and controls appears good based on their very similar age distributions, matching on hospital and age, and restriction to nonsmokers, although the lack of further demographic comparisons means that divergence on some other factor(s) cannot be ruled out.

A major difficulty in this study, however, arises from the extensive use of proxy respondents. Only 12% (16 of 134) of the case interviews were with the patient. In the stratified analysis, it was found that the husband's smoking at home is positively associated with lung cancer only when the smoking information is provided by a son or a daughter rather than by the patient or her husband. This leads to several possibilities. Perhaps the son or daughter claimed that the patient's husband smoked when he actually did not, thereby shifting cases from the nonexposed to exposed category and increasing the odds ratio, or the patient or her husband claimed that the husband did not smoke when actually he did, thereby shifting cases from the exposed to nonexposed category and depressing the odds ratio. In general, it is thought more likely that true smokers are misclassified as nonsmokers more often than true nonsmokers are misclassified as smokers (see, for example, Lee, 1986, and Machlin et al., 1989). Also, Machlin indicates that proxies tend to misclassify smokers no more often than smokers themselves do. Thus, it may be that the son or daughter data are better than the self or husband data. Alternatively, the difference among the reporting sources may be due only to chance; the results in JANE on self or proxy reports are quite the opposite of those in this paper, with the proxy reports (in this case including the spouse) leading to lower odds ratios than the self-reports.

Another possible problem with this study is the use of colon and rectal cancer cases as controls on the theory that these diseases are not smoking related. A recent paper, Zahm (1991), notes that associations have been found between smoking and these cancers. If these associations carry over to passive smoking, they might bias the result downward.

In general, the detailed results from the stratified analysis in Table 6 of the paper exhibit considerable variation, probably caused by chance. Hence, the overall results in Table 5 of the article, where all the cases and controls are used, may be the most reliable. They indicate an odds ratio of 1.31 (1.24 after adjustment for smoker misclassification bias in the body of this report) for exposure to all types of husband's smoking at home.

The study's exposure assessment methodology is strengthened by the attempt to maintain blinding by not informing interviewers of the study hypothesis or the subjects' disease status. This is impractical in most studies, but given the use of controls who also have cancer and a high

proportion of proxy interviews, effective blinding of interviewers *and* subjects may have been largely achieved here. Detailed data on smoke exposure at home as well as elsewhere, including pipe and cigar smoking, were collected. Pipe and cigar smoking are often not considered in ETS studies, thus constituting a potential source of exposure misclassification, and smoking at home should be a more meaningful index of smoke exposure than total smoking. What the authors termed "husband's smoking" actually includes smoking by related cohabitants as well. Presumably, this was done both to increase subject numbers (by not excluding unmarried women) and to enhance detection of passive smoke exposure. However, it could cause some oversight with regard to classification of ETS exposure (e.g., a widow, living with a nonsmoking sister, whose husband had been a heavy smoker). Less understandable is the failure to include smoking by *un*related cohabitants and the inclusion of single women living alone. Diagnostic misclassification is unlikely given the histological verification of all cases *and* controls.

Both husband's at-home and total cohabitant smoking are associated with lung cancer, the association being stronger for at-home smoking. Both exposures show a statistically significant general increase in association with level of smoking, with substantial associations only at high levels. The adjusted association for at-home cohabitant smoking is much stronger (OR = 1.7; p = 0.03) than that for smoking outside the home (OR = 1.3; p = 0.13), a pattern consistent with home smoke exposure rather than some other smoking-related factor as the basis of the observed results. General ETS exposure, in contrast, was inconsistently related to lung cancer in the unadjusted analyses, with a stronger association for exposure within the last 5 years than within the last 25 (possibly attributable to better recall). No dose-response pattern is evident, however, and no association was found in the adjusted analyses.

The adjusted analyses include age, hospital, socioeconomic status, and year of diagnosis in a logistic regression model, along with the passive smoking variable. This adjustment did not significantly reduce the association between husband's smoking at home and lung cancer observed before the adjustment, but it did eliminate any association with general ETS exposure. Thus, the results for husband's smoking at home are probably not biased due to influences of age, socioeconomic status, hospital, or temporal variables. Dietary factors, heating and cooking practices, and family history of cancer were not considered as modifying risk; thus, an effect by one or more of these factors cannot be ruled out.

The heavy reliance on proxy respondents and their uncertain impact on the analysis leaves some uncertainty in interpretation. On the favorable side of this issue, the authors' attempt to blind subjects and interviewers to the study hypothesis lessens the likelihood of potential bias from proxy response, and no significant effect due to respondent type was found in the adjusted

analyses. Some of the exposure categories seem vague, but this would tend to reduce the magnitude of the observed association rather than to give rise to one. In summary, this study is suggestive of a dose-dependent association between smoking in the home and lung cancer, with reservations due to the use of proxies.

A.4.10. GARF(Coh) (Tier 3)

A.4.10.1. *Author's Abstract*

"Lung cancer mortality rates were computed for nonsmokers in the American Cancer Society's (ACS) prospective study for three 4-year periods from 1960 to 1972 and in the Dorn study of veterans for three 5-year periods from 1954 to 1969. There was no evidence of any trend in these rates by 5-year age groups or for the total groups. No time trend was observed in nonsmokers for cancers of other selected sites except for a decrease in cancer of the uterus. Compared to nonsmoking women married to nonsmoking husbands, nonsmokers married to smoking husbands showed very little, if any, increased risk of lung cancer."

A.4.10.2. *Study Description*

This study examines the role of passive smoking in lung cancer among married women in the United States. It uses data collected in a large prospective study initiated by Cuyler Hammond of the ACS in 1959. The ACS's objective was to evaluate the association between potential cancer risk factors and cancer mortality. Although data were collected on the smoking status of women and their spouses at the start of the study, Hammond thought the study data should not be used to estimate lung cancer death rates in relation to amount of passive smoking by female never-smokers. Specifically, Hammond notes that the study was not designed for that purpose, and no special information on the subject was obtained; information was available on the smoking habits of the husbands of many of the married women in the study, but not on the smoking habits of the former husbands of women who were widowed, divorced, separated, or married for a second time. More important is his statement that women in America at that time were not generally barred from public and social gatherings where men were smoking, and working husbands who smoked generally did much if not most of their smoking away from home (Hammond and Selikoff, 1981). Similar reservations are expressed by Garfinkel, who also notes that 13% of the women nonsmokers who died of lung cancer in the ACS study reported that they were previously married and that the classification of their exposure to their husbands' smoking may not be pertinent (Garfinkel, 1981, p. 1,065).

A total of 29 ACS divisions encompassing 25 states took part in the study; participating counties were in turn selected by division leaders based on feasibility. Data collection was undertaken by networks of volunteers set up within participating counties. Recruitment of subjects and subsequent followup monitoring were undertaken by volunteers who were instructed to enlist qualifying acquaintances. Subjects were restricted to persons more than 30 years of age whose household contained at least one person over 45 years of age. Illegal immigrants and persons who were illiterate, institutionalized, or itinerant were excluded. Detailed questionnaires were distributed to subjects and all members of their household over 35 years of age. These questionnaires covered factors such as diet, alcohol consumption, and occupational exposures as well as smoking habits, but they did not address passive smoke exposure. Volunteers who recruited subjects were given responsibility for tracing the subject's vital statistics for the next 6 years and contacting living subjects again in 1961, 1963, and 1965 to complete a questionnaire on changes in smoking habits. Alternate researchers were appointed as necessary to replace volunteers who moved or quit. Finally, death certificates were obtained for subjects reported deceased; where death due to cancer was indicated, verification was sought from the certifying physician. Although followup initially ceased with 1965, in 1972 an additional followup was initiated in 26 of the original 29 ACS divisions and terminated in September 1972.

A.4.10.3. *Comments*

The passive smoking study being described was undertaken by assembling a subcohort of married women who reported that they had never smoked and whose husbands completed a questionnaire including smoking habits. This subcohort totaled 176,739 women out of the 375,000 never-smoking women enlisted by the ACS in 1959. Women were divided into three exposure categories based on their husband's smoking status--nonexposed for never-smokers, and low (high) for current smokers of less (more) than 20. Wives of former cigarette smokers and men who smoked cigars or pipes rather than cigarettes were excluded (Garfinkel, 1984); presumably, these had already been excluded from the reported total (176,739). Mortality rates were computed by 5-year age intervals for unexposed women (i.e., wives of nonsmokers), from which the expected number of deaths for exposed women was estimated under the hypothesis that spousal smoking does not affect lung cancer mortality. The ratio of observed to expected deaths in the exposed group provides an age-standardized mortality ratio. This mortality ratio is 1.27 (95% C.I. = 0.85, 1.89) for spousal smoking of under 20 cigarettes per day (low exposure) and 1.10 (0.77, 1.61) for over 20 cigarettes per day (high exposure).

In a separate analysis, women healthy at the start of followup were divided into groups matched on age (5-year grouping), race, education, urban or rural residence, and occupational exposure of husband to dust, fumes, or vapors. Each of these matched groups was then subdivided into zero, low, and high exposure categories. The proportion of observed deaths in each category was multiplied by the proportion of subjects in the smallest category of the matched group relative to that category. This "adjusted" number of deaths was then summed across all groups with a given exposure and compared with the corresponding value for the unexposed (zero exposure) category to provide a mortality ratio. In addition, we conducted a Mantel-Haenszel analysis of mortality using data supplied by Garfinkel that yielded results similar to the author's analyses. Ages 35 to 39 and 70 to 79 were excluded due to insufficient numbers. After stratifying by age and correcting for time under study, the calculated lung cancer risk was greater in subjects whose husbands smoked, but the predicted risk at low exposure was greater than at high exposure. It is notable, however, that the lower risk at higher exposure is entirely attributable to the 50- to 59-year-old age group; otherwise, predicted mortality would be equivalent at the low and high exposure (see Table C-1 of the report under discussion).

The original ACS cohort study was a massive undertaking. By using it as the basis of his cohort, Garfinkel was able to assemble a very large number (more than 170,000) of never-smoking married women. A cohort of this magnitude attains a number of lung cancer cases ordinarily feasible only by means of a large case-control study, while avoiding the attendant pitfalls of potential recall and interviewer bias associated with case-control studies. There are several important limitations, however, that make the results of this study difficult to interpret. The ACS study was not designed to yield a representative sample of the general population. The sample of women is older (all at least 35 years of age, two-thirds between 40 and 59 at start of followup), more educated (only 5.6% were limited to a grade school education), and contains a much smaller proportion of ethnic minorities (only 6.8% nonwhite) than the general population (Stellman and Garfinkel, 1986). Although not representative of the population as a whole, the relative homogeneity of the subject population does reduce the potential for complications of interpretation that differences in ethnic or socioeconomic factors or both may pose, and it increases efficiency by not including subjects belonging to age groups unlikely to experience significant mortality during followup. Overall, the study population's unrepresentativeness strengthens rather than undermines the study's conclusions. It would have been useful, however, to confirm that exclusion of greatly underrepresented groups, such as nonwhites and persons with no formal education beyond the eighth grade, had no effect on the results.

Because the data on smoking habits were collected prospectively, no information on exposures prior to 1959 was obtained. Exposure history for the years before 1959 may be as

important as for the 12 years of followup, however, if lung cancer has a long latency period, such as 20 years or so. Inclusion of persons whose exposure status may have changed markedly by 1959 could be a biasing influence. Neither were changes in exposure status during the followup period considered, despite the availability of data on smoking habits in 1961, 1963, 1965, and 1972. In fairness to the author, keep in mind that our comments are directed at evaluation of the study for its contribution to the issues of passive smoking and lung cancer, although the ACS study was not designed to assess ETS exposure. The only data collected on ETS exposure are based on the spouse's *current* smoking habits at initiation of the study. If the ACS study had been directed at evaluation of health effects of ETS, these issues would likely have been taken into consideration to sharpen the classification of subjects with respect to ETS exposure. Overall, the likely consequence of these factors is to reduce the sensitivity of the study to detect an association between lung cancer and ETS exposure, but the potential for bias in the direction of a false positive cannot be ruled out. For example, if wives of smokers are more likely to become active smokers during followup than wives of nonsmokers, these changes in smoking status could bias results toward finding a positive association with passive smoking. (Relevant to this particular example, the authors state that "very few" subjects reported a change in their smoking status, but provide no further details. Also, 12 or fewer years is a short exposure to produce lung cancer. It is thus probable that any bias introduced by active smoking would be minor; furthermore, the fact that a stronger association was observed for low than for high levels of spousal smoking argues against a confounder associated with spousal smoking. Nevertheless, potential sources of bias may be present that influence the study outcome in either direction.)

During 1959-65, confirmation of primary lung cancer diagnosis was obtained from physicians for 78% of all cancer cases. Among 203 cases of lung cancer in nonsmoking women diagnosed by death certificate, confirmation attempts on an unspecified number of these cases found 34 misdiagnosed as primary lung cancer, whereas 10 primary lung cancers were discovered among cancers diagnosed as nonlung on death certificates. Thus, it appears that only about 85% of the death certificate diagnoses of primary lung cancer were accurate, while a small percentage of primaries were misdiagnosed as cancers of other sites. No confirmation of diagnoses was undertaken during the period after 1965 when nearly two-thirds (119 out of 182, according to data supplied to reviewers by Garfinkel) of the lung cancer deaths in the ETS study population were reported. In light of the misdiagnosis rates found for 1959-65, it is likely that a substantial percentage of the study's reported primary lung cancers in cases actually arose in other sites, whereas a substantial percentage of reported cancers of other sites actually arose in the lung. The

resultant errors in subject classification probably bias the results toward no association (i.e., a false negative conclusion), *if* a positive association actually exists.

Loss of subjects to followup is another source of potential bias. A subsequent report on the ACS cohort (Garfinkel, 1985) states that, whereas more than 98% of the original cohort was successfully traced through 1965, more than 10% (3 of 29) of the original ACS divisions declined to participate in the 1971-72 followup effort. In the study now under review, Garfinkel reports successful followup of 98.4% through 1965 and 92.8% through 1972, apparently not considering subjects in the division who declined to participate in the extended followup as losses. It thus appears that, whereas more than 98% of the original cohort was successfully followed up through 1965, less than 90% of the cohort was targeted for followup through 1972, and losses for this targeted group approached 7%. Such losses not only reduced the number of observed deaths--and, hence, the study's power--but introduced the possibility that differential loss to followup could have distorted the study's results. A greater proportion of losses among exposed subjects than among unexposed could partially mask a true positive association, whereas greater loss among the unexposed could potentially create a spurious association.

Aside from the issues above, the study controls for risk modifiers. Subjects were all of the same gender and marital status, and age was controlled for in all analyses. Analysis by groups matched on race, education, residence, and occupation, along with age, produced nearly identical results as the analyses standardized by age alone, indicating no confounding due to these and unlikely confounding due to other socioeconomic, occupational, or geographic factors.

In summary, this study predicts a weak positive association between spousal smoking at levels of 1 to 19 cigarettes per day and lung cancer, but only slight association at higher exposure levels; neither association is statistically significant. The lack of apparent dose-response pattern undermines the association, but the confidence intervals of the point estimates for the high- and low-exposure groups overlap so broadly that the existence of a dose-response relationship cannot be ruled out entirely. Meaningful interpretation of the results for the issue of ETS exposure and lung cancer, however, is limited. Because the study's objectives were directed elsewhere, the data collected on ETS exposure are limited to the status of spousal smoking at the start of the study. Past history and future changes in status are not well addressed. There is ample indication that death certificate diagnoses are not a reliable source for the selection and classification of subjects. Although a second 6-year followup period was undertaken to increase the followup period to 12 years, its success was limited by incomplete participation and, perhaps, by organizational difficulties related to long-term reliance on volunteers (who may relocate, change interests, lose contact with the subjects originally enlisted over an extended period, etc.). Even if the followup

were entirely successful, however, 12 years of followup without regard to exposure experience is not a particularly long period to evaluate the lung cancer potential for ETS because the latency period associated with active smoking may be on the order of 20 years. Although the ACS study has been an important contribution to its main study objectives, the limited exposure information and other potential sources of bias for the issue of passive smoking and lung cancer leave its assessment in question.

A.4.11. GENG (Tier 4)

A.4.11.1. *Author's Abstract*

Not included in source.

A.4.11.2. *Study Description*

This study was conducted in Tianjin, where China's highest incidence of female lung cancer occurs, to illustrate the relationship between cigarette smoking and lung cancer in females. The study explores both active and passive smoking, so the analyses for passive smoking apply to a subgroup of the larger subject population. The source of the study's subjects and the time over which they accrued are not specified. Subjects resided in Tianjin for more than 10 years. The source of controls is not given, but they consist of females pair-matched with cases on race, age (± 2 years), marital status, and birthplace. It is unclear from the article whether cases were incident or prevalent and how controls were obtained. A draft summary description of this study (Liang and Geng, undated) from Liang indicates, however, that hospitalized cases (96) were matched with inpatient controls and that general population cases (61) were matched with neighborhood controls.

The source of the study's exposure data is not clearly stated, but the draft from Liang indicates that all identified cases and controls were interviewed. No information on collection or verification of smoking or other data is provided. The authors state that cases and controls do not differ significantly in age, education, occupation, race, marital status, birthplace, or residence, but this refers only to the total study population of 157 cases and 157 controls that includes active smokers; the same similarity may not hold for the 54 cases and 93 controls used in the passive smoking analysis. Tumor types are provided for 85% of the total case population but not specifically for the passive smoking subpopulation; adenocarcinomas (36.9%) predominate, being about twice as common as squamous (22.3%) or small cell (19.7%) tumors. Although nearly 85% of the total cases were diagnosed histologically or cytologically, it does not appear that verification of

diagnosis or primary status of tumor was undertaken by the authors, and no information on tumor distribution is supplied.

A nonsmoker (which usually means never-smoker) is ETS exposed if the spouse smokes. Presumably, women not currently married are excluded from the analysis, although they could have been included with some assumption made regarding their exposure status. Information on dose and duration of exposure was collected but not used in the passive smoking analysis, and it is not indicated if cigar or pipe smoke was included. ETS exposure from parents and colleagues is reported to have been evaluated. The parental smoking referred to is apparently in adulthood, as cohabitants in the home, but that is not made explicit. Exposure during childhood was not specifically addressed.

Among the ETS subjects, 34 of 54 cases and 41 of 93 controls were exposed. This yields a statistically significant crude odds ratio of 2.16 (95% C.I. = 1.03, 4.53) for husband's smoking. No analyses adjusted for age or other factors are reported. On a rather confusing note, an odds ratio of 1.86 is cited twice later, but that value is inconsistent with the odds ratio of 2.16 from the raw data. Whether this is an error or the product of an unspecified adjustment by conditional logistic regression, which the authors employ for other purposes throughout the paper, is unknown. The odds ratio increases with the number of cigarettes smoked per day by the husband and with the duration of the husband's smoking. The odds ratios for smoking rates of 1 to 9, 10 to 19, and 20 or more cigarettes per day are 1.4, 2.0, and 2.8, respectively. For 1 to 19, 20 to 39, and 40 or more years of exposure, the odds ratios are 1.5, 2.2, and 3.3, respectively. No tests for trend are cited, and the relevant data are not given. Consideration of ETS exposure from smoking by father, mother, or "colleagues" reportedly yielded no results that are "quite significant." No further details are provided, and it is not clear whether these results consider past smoking status or apply only to current status.

The authors conclude that active and passive smoking are the most important risk factors for female lung cancer in Tianjin. They attribute 35% to 42% of lung cancer occurring in their nonsmoking female population to passive smoking. Female lung cancer also is found to be associated with other factors, such as occupational exposure, with an odds ratio of 3.1 (95% C.I. = 1.58, 6.02); history of lung disease, with an odds ratio of 2.12 (95% C.I. = 1.23, 3.63); and cooking with coal, where the odds ratio increases with the duration of exposure from 1.5 to 5.5 (see Table 8 of this reference).

A.4.11.3. *Comments*

The quality of this study is difficult to assess given the dearth of details supplied by the authors. Certainly the number of nonsmoking cases and controls included is more substantial than in some other studies, and the reported association between passive smoking and lung cancer is statistically significant. Questions regarding the mechanics of data collection and analysis, however, remain unanswered.

Exposure and other data were obtained from hospitalized subjects at bedside and from others in their homes. Apparently no information was obtained from proxy sources; the number of cases (or controls) who could not be interviewed is unspecified. No blinding was employed, but that may not have been feasible. Despite the reported similarity of the demographic characteristics of the total case and control populations, dissimilarity cannot be ruled out within the subgroup used for ETS analyses. Although the whole study, including active smokers, is matched on several variables, that matching need not apply to the ETS subjects alone.

Lack of validation of diagnostic and exposure information may have led to substantial misclassification, although the fact that 85% of the lung cancer diagnoses were obtained via histology or cytology suggests that diagnostic misclassification would not have been extreme. Lack of consideration of former smoking status is a potential problem. Inclusion of former smokers among the nonsmokers, in combination with a tendency for former smokers to marry smokers, could produce an upward bias in the odds ratios.

Finally, although the crude odds ratio of 2.16 for passive smoking is statistically significant, it does not take into account even the most basic potential confounder--age. For the larger case-control population (including smokers), occupational exposure (OR = 3.1), history of lung disease (OR = 2.64), and cooking with coal (OR = 1.54-5.56, rising with cumulative exposure) are statistically significant risk factors that the authors claim have joint effects with smoking, yet the ETS analysis is not adjusted for these likely confounders. The anomalous odds ratio of 1.86 given later in the results *may* have been adjusted for age or other factors, but there is no way to tell. Also, the detection of an effect of ETS would be unexpected if the study area suffered from high environmental levels of carcinogenic combustion products of coal, as seen in LIU and WUWI. Although the literature contains no studies of Tianjin, Beijing is nearby. Zhao (1990) reports that mean levels of a urinary indicator of polyaromatic hydrocarbon exposure (1-HP) in nonsmoking housewives are much lower in Beijing than in Shenyang, one of the WUWI study sites, but Wang (1990) found that indoor air pollution, principally due to coal burning, sometimes masks the effect of *active* cigarette smoking.

After standardization for age and occupation, it was found that women whose husbands smoked daily had a higher annual rate of lung cancer mortality than did women whose husbands were nonsmokers or only "occasional" smokers. The rate increased with the level of smoking (e.g., 8.7/100,000 annually for no or occasional smoking, 14.0 for smoking 1-19 cig./day, and 18.1 for 20+ cig./day). Higher rates and a dose-response pattern were observed in women married to smokers after stratification on either husband's age or agricultural work status. Mortality due to two diseases associated with active smoking, emphysema and asthma, was also higher in wives of smokers and increased with exposure. Conversely, mortality due to two cancers not linked to active smoking, cervical and stomach cancer, was no higher in wives of smokers. Consideration of husbands' drinking habits had no significant impact on mortality for lung cancer or other diseases mentioned above.

Further study results appeared in the October 3, 1981, issue of the *British Medical Journal*. Among other things, results were presented by husband's age in 10-year intervals instead of 20-year intervals and for 10 occupational categories instead of 2. These tabulations revealed a statistically significant overall association between husbands' smoking and lung cancer mortality with a dose-response pattern (1.00 RR for nonsmokers plus former smokers, 1.44 RR for medium smokers, and 1.85 RR for heavy smokers). Also of interest was a breakdown of lung cancer mortality and smoking habits in greater detail for both husband and wife. Notably, nonsmoking *husbands* with smoking wives showed a higher lung cancer mortality rate (RR = 2.94) than did those with nonsmoking wives. Because nonsmoking husbands with smoking wives were rather rare, however, the numbers in this stratum were low (only seven deaths); thus, the observed association was not statistically significant.

In 1984, Hirayama published results of an additional 2 years of followup of his cohort in *Preventive Medicine*. The same basic associations reported after 14 years of followup for spousal smoking and lung cancer remained after 2 additional years of followup. Mortality rates increased with increasing exposure after stratification by age of husband, occupation, geographical area, and time period during study; a trend had been reported after stratification for age of wife at start of study only for ages 40 to 49 and 50 to 59. It also was reported that the elevation of lung cancer mortality in nonsmoking women married to smokers was significantly less among women who consumed green-yellow vegetables daily (e.g., for spousal smoking of 20+ cig./day, the RRs for disease mortality were 1.63 and 2.38). No such pattern was observed for ischemic heart disease. In addition, a statistically significant excess of para nasal sinus cancer in nonsmoking wives of smokers had been observed, which showed an apparent dose-response relationship across four smoking categories, culminating in an RR of 3.44 for spouses of smokers of more than 20

In summary, the study's results are consistent with the hypothesis that passive smoking increases the risk of lung cancer, but they are not definitive. More detail regarding the mechanics of the study is needed to assess its general validity. If warranted, a clearer and more complete analysis of the study's data regarding passive smoking, including consideration of the information on dose, duration, and potential confounders already available, would then be useful. For the current evaluation of epidemiologic evidence on ETS exposure and lung cancer, too many questions remain about the design and execution of the study to properly interpret the data and assess the authors' conclusions.

A.4.12. HIRA(Coh) (Tier 2)

(*Note*: Because of the many publications relating to this study, a different format of presentation is used.)

This cohort study and a later case-control study based on it were undertaken to explore the relationship of passive smoking and other factors with lung cancer in Japanese women. Subjects and data used in this study were, however, drawn from a larger study that was not designed to investigate passive smoking.

An exploratory study of mortality determinants targeting adults at least 40 years of age inhabiting 29 health center districts in Japan was initiated in 1965. In autumn of 1965, more than 90% of the target population was interviewed to ascertain the status of lifestyle factors that might affect health (e.g., cigarette smoking, alcohol consumption, and occupation). Individuals, including husbands and wives, were interviewed separately. Followup of the interviewees was conducted using a combination of an annual census of residents and death certificates to monitor mortality. Mortality, as determined by death certificate, was the outcome variable. Hirayama used this study population to examine the potential effect of passive smoking on lung cancer mortality. In 1981, he reported the results derived from the first 14 years of followup (through 1979) in the *British Medical Journal*.

A total of 142,857 women were interviewed in 1965, of whom 91,540 were nonsmokers whose husbands also had been interviewed regarding smoking status. Using their husbands' smoking status as a surrogate for exposure to ETS, Hirayama calculated lung cancer mortality rates for comparison of women married to smokers with women married to nonsmokers; rates also were calculated using various strata of spousal smoking intensity (number of cig./day), as well as age and occupation. A total of 346 lung cancer deaths occurred in this cohort during the first 14 years of followup.

cigarettes per day. That effect dwarfed those related to social class and dietary factors that were also examined.

In 1988, Hirayama reported the results of a case-control study nested within his cohort in *Environmental Technology Letters*. To explore the relationship of women's age at marriage as well as husbands' smoking status with lung cancer mortality, lung cancer cases occurring among nonsmoking women in the cohort study were contrasted with stomach cancer cases as controls. Including only women under 59 years of age at the start of the cohort, the study divided husbands' smoking into three categories--none, 1 to 19, and 20 or more cigarettes per day. Age at marriage also was trifurcated in 19 or fewer, 20 to 23, and 24 or more years. Apparently as a result of exclusion of women over the age limit or because of missing data, only 115 cases and 423 controls were ultimately compared out of the 200 lung cancers and 854 stomach cancers among the nonsmoking female cohort. Adjusting for woman's age and husband's smoking category resulted in odds ratios for lung cancer of 4.95, 1.76, and 1.41 for the respective age-at-marriage groups; the first two of these odds ratios were statistically significant. An additional comparison found that among lung cancer cases, the mean age at first marriage to a smoking husband was nearly 8 years less than the mean age at start of smoking for active smokers.

A greatly expanded nested study was presented in the following year (Hirayama, 1989). The study was designed to explore the potential effect of dietary habits on the relationship between lung cancer and spousal smoking. A "baseline" sample of 2,000 nonsmoking wives, aged 40 to 69 at the start of the cohort study, with known spousal smoking habits was randomly selected from the available cohort of 90,458 for comparison with the 194 lung cancer cases occurring in equivalent subjects within the cohort. After determining that the age distributions of the case and baseline groups were very similar within smoking categories, the combined population was stratified on daily versus less-than-daily consumption for each of five food types (green-yellow vegetables, fish, meat, milk, and soybean paste soup), and wives with smoking and nonsmoking husbands were contrasted to assess differences in dietary habits. After adjustment for wife's age and husband's occupation, only daily meat consumption was significantly more common among wives of smoking husbands, and this was limited to smokers of 20 or more cigarettes per day. Calculation of odds ratios for dietary habits resulted in a "significant" elevation only in daily fish consumers (OR = 1.365, 90% C.I. = 1.05, 1.77; Table IV). A nearly significant *lowering* of the odds ratio was found in daily meat consumers.

Finally, odds ratios were calculated for lung cancer adjusted by wife's age, husband's occupation, and each of the dietary habit categories in succession. A dose-response pattern was observed between lung cancer and husband's smoking that persisted after adjustment for any of

the five dietary factors. Odds ratios for the five dietary habit categories ranged from 1.42 to 1.69 for former smokers and smokers of 1 to 19 cigarettes per day and from 1.66 to 1.91 for smokers of 20 or more cigarettes per day compared with nonsmoking husbands. The observed trend was highly statistically significant, regardless of which factor was adjusted for in the calculation.

A.4.12.1. *Chronology of Controversy*

Publication of Hirayama's initial 14-year followup results in 1981 provoked a sizeable volume of commentary in the scientific literature. Following the release of updated results in 1983-84, the study attracted little controversy until the latter part of the 1980s, when criticisms were directed at the study by a number of authors. This process reached its culmination in response to the EPA's release for external review of the document *Health Effects of Passive Smoking: Assessment of Lung Cancer in Adults and Respiratory Disorders in Children*, which placed considerable emphasis on Hirayama's results. An author-by-author, letter-by-letter consideration of the arguments regarding Hirayama's work would be dauntingly duplicative and tedious. Instead, the most-discussed concerns are highlighted below, followed by an overall assessment of the study as it stands today.

Chronology of Selected Events Relevant to the Hirayama Cohort Study

Jan. 7, 1981	Results of cohort study are published in *British Medical Journal* (282:183-185).
Oct. 3, 1981	Comments and letters to the editor by Kornegay and Kastenbaum (of the U.S. Tobacco Institute), Mantel, Harris, and DuMouchel, and MacDonald regarding Jan. 7 article appear in *British Medical Journal*, along with the author's reply.
March 3-5 and July 10-15, 1983	Hirayama presents updated results for his study cohort incorporating an additional 2 years of followup (for a total of 16 years) to the International Lung Cancer Update Conference in New Orleans and the 5th World Conference on Smoking and Health in Winnipeg, Canada.
Dec. 17, 1983	Updated results of the cohort study are published in *Lancet*.
1984	Results presented in conference of July 1983, and in summary form in *Lancet* later that year, are published in full in *Preventive Medicine*. In addition, Hirayama now reports a statistically significant increase in brain tumors with husbands' smoking. In a roundtable discussion published in the same journal, Lee proposes that misclassification of active smoking status may have biased Hirayama's results.
1985	Another publication of results for the 16-year followup appears in *Tokai Journal of Experimental Clinical Medicine*.
1987	Hirayama includes previously published study data in a book chapter (Aoki et al., 1987).

1988 Uberla and Ahlborn publish an article from the *Proceedings of the Indoor Ambient Air Quality Conference* in London (which is essentially the same as an earlier presentation at the 1987 Tokyo International Conference on Indoor Air Quality) criticizing the Hirayama study on several grounds. Their primary assertion is that correction for the cohort's age distribution removes the apparent effect of spousal smoking.

1988 Hirayama publishes the results of nested case-control study based on cohort study data in *Environmental Toxicology Letters*. Estimated risk of lung cancer is reported to increase with earlier age of marriage to smoker.

1989 Layard and Viren publish a paper presented at the Conference on the Present and Future of Indoor Air Quality in Belgium. Making their own projections of expected deaths and estimating losses to followup, they conclude that mortality rates were anomalously low and followup losses unacceptably high in the Hirayama study.

1989 Hirayama publishes nested case-control results in *Present and Future of Indoor Air Quality*. Positive association of husband's smoking and lung cancer with dose-response pattern is reported after adjustment for dietary variables.

A.4.12.2. Some Major Critical Works

A basic point raised by MacDonald (1981) and others soon after publication of Hirayama's initial results concerned the selection of the study's sample population. It appeared that the 29 health centers included in the study were selected on grounds of convenience rather than to provide a randomly sampled, representative cross-section of the Japanese population. The resultant sample might thus be unrepresentative of the Japanese population as a whole.

Hirayama replied in 1981 that "the satisfactory representativeness [of the study population] . . . with regard to demographic and social indices was confirmed after the survey." He did not, however, provide supporting data. MacDonald (1981) contended that the six prefectures from which the sample was drawn are relatively industry-heavy. Hirayama (1983a) presented data showing that 40,390 of the cohort's wives were married to agricultural workers, 19,264 to industry workers, and 31,886 to "others," indicating some overrepresentation of *agricultural* areas. He later (1990b) cited quality of incidence data, geographical diversity, and coverage of communities of both urban and rural character as well as different dominant industries as key selection criteria. Women aged 70 or more are clearly underrepresented, composing less than 1% of the study's 40-and-older nonsmoking female population; this aspect of the study will be addressed later.

The key problem arising from an unrepresentative sample is that it may limit generalizability of results derived from that sample to the population as a whole. In lieu of good reasons to think that the association between exposure and disease would be different in the study population and the general population, however, the possibility of an unrepresentative sample

assumes less importance. Further, in this case, substantial numbers from each major geographical and occupational element of the general population *were* included in the sample. And, as will be seen in the subsequent discussion, similar patterns of association were observed in a number of demographic subgroups.

Misclassification may occur in any epidemiologic study. Most of the critical commentary has focused on potential misclassification of exposure status. Because the study relies on interview data to establish smoking status, misreporting by interviewees may affect accurate classification of both wives *and* their husbands' smoking habits. It has been argued that women are especially likely to misrepresent their smoking habits because smoking is considered less socially acceptable for women than for men, particularly in Asian societies. Such misclassification would tend to reduce the degree of association between passive smoke exposure and its effect(s) if women in the "exposed" and "unexposed" groups were equally likely to misreport their own smoking. One of the most prominent criticisms leveled at the Hirayama study postulates a differential misclassification of smoking status in women. Peter Lee (Lehnert, 1984) raised the argument that if women married to smokers are more likely to be (or to have been) smokers than women who are married to nonsmokers, and a given percentage of smoking women claim to be nonsmokers, then purportedly nonsmoking wives of spousal smokers will include a higher proportion of active smokers than wives of spousal nonsmokers. This will cause bias in the direction of a positive association. Arguments over the probable size of this bias have occurred with estimated elevations in risk ranging from a few percent to around 50%, depending on assumptions regarding the extent of misreporting, the risk inherent in active smoking, and the degree of marital concordance between smokers (Lehnert, 1984; Wald et al., 1986; Lee, 1987a, b).

Uberla and Ahlborn (1987) raised a number of points regarding the Hirayama study, including those previously mentioned. Citing the "severe selection bias by age," the authors report that the increase in risk with spousal smoking disappears when this bias is corrected for. The study population in fact contained a very small proportion of women aged 70 or older (only about 1%)--so small that the rates generated by nonsmoking married women aged 70 or older are too unstable to provide meaningful results. But by taking the negative results observed in this tiny, unstable stratum of the cohort and weighting them to "correct" for the underrepresentation of this age group, the overall association is made to disappear. Such a "correction" is meaningless. In addition, Hirayama (1990b) has noted that the authors inappropriately adjusted to the total female population rather than to the population of currently married females, and he characterized the adjustment as "neither of scientific significance nor of creative value."

The authors also essentially take Lee's approach to the differential misclassification problem and claim that a modest differential misclassification "leads to risk ratios of around unity." As seen previously, this argument is plausible but purely speculative--and potential biases toward the null are ignored in this and other "corrections." The authors conclude that "the null hypothesis . . . is consistent with the Hirayama data in the same way as is the alternative." But unless one applies the aforesaid "corrections," the Hirayama data are, in fact, *more* consistent with the hypothesis of association than with the null hypothesis.

Layard and Viren (1989) estimated "projected" mortality rates for a cohort with the age and time distribution found in the Hirayama cohort by applying "standard demographic life table procedures" to year- and age-specific life table data from United Nations and Japanese sources. They concluded that female all-cause and lung cancer reported rates were only 76% and 85%, respectively, of projected values. In a separate analysis, the authors also "calculated the numbers of person-years that would have been observed in the cohort if there had been 100% followup" from the reported numbers of deaths. The assumptions used in this calculation are unstated. The authors then estimated, based on the difference between their person-years for 100% followup and the reported person-years, and an assumption that 8 years of observation were lost on average for each person lost to followup over the 16-year course of the study, that approximately 10% of the cohort was lost to followup. Dismissing other possible causes of their estimated mortality deficits, Layard and Viren conclude that "it is possible that biases exist in the data which might invalidate an observed relationship between exposure to ETS and mortality."

Acceptance of Layard and Viren's conclusions must start with acceptance of the validity of their assumptions and calculations, not all of which are stated explicitly. Beyond that, their rejection of alternative explanations for the difference between projected and reported deaths is not convincing. For example, random sampling variation and regional variations in death rates are both dismissed because neither could produce an effect as large as that observed, although the authors' figures indicate that in combination they could well account for a sizeable portion of the difference. Likewise, the effect of admitting only (initially) "healthy" people to the cohort is dismissed based on the observation of "still very substantial cohort deficits in the last years of the study" without specification of how substantial such deficits were and ignoring the fact that a pattern in which all-cause mortality is most affected and cancer mortality least, as their calculations showed, is the expected pattern for an effect of selection of healthy individuals. Finally, to produce a spurious association, a bias must operate differently on the exposed (smoking spouse) and unexposed (nonsmoking spouse) groups, and no evidence is provided that supports such a pattern. In fact, Hirayama (1990b) reported an approximately 8% loss to followup for the

whole cohort, which did not differ significantly by male smoking status. Lacking a pattern of differential loss, the most likely effect of loss to followup is a reduction in the observed associations due to missing mortality events. The effect of selecting an abnormally healthy cohort would in a strict sense limit generalizability of conclusions but would not in itself produce an exposure-effect association when none actually existed.

A.4.12.3. *Critique and Assessment*

Hirayama's cohort is drawn from a study population assembled to explore the associations between a number of potential health-influencing factors determined via interview and subsequent mortality. Thus, the study was not designed to investigate passive smoking and lung cancer specifically. Most of the weaknesses attributable to Hirayama's study derive from this fact.

The only indicator of ETS available to Hirayama was self-reported smoking status at time of baseline interview. Thus, misclassification of spousal smoking status is possible, and change in status over time, modifiers of exposure to spousal smoking, and other sources of ETS exposure cannot be determined.

As previously seen, an overrepresentation of current and former active smokers claiming to be nonsmokers among wives of tobacco smokers probably biases the association between spousal smoking and lung cancer in reported nonsmokers upward. Even the leading proponent of this argument, however, states that unless this bias is much stronger than it appears to be in U.S. and Western populations, it could not account for the major part of the observed results (Lee, 1990). Lack of information regarding the amount of smoking actually done in the home and in the presence of the spouse, room size and ventilation, and other exposure-modifying factors must lead to imprecision in the estimates of exposure via spousal smoking. This imprecision would make an actual ETS-lung cancer association more difficult to detect. The fact that spousal smoking exposure, even if precisely measured, is an imperfect surrogate for total ETS exposure because workplace and ambient environmental sources are not assessed introduces a similar effect. Both of these problems would thus introduce a bias toward the null, suggesting that the study's results are an underestimate of the real association.

Mortality information was derived from death certificate linkage. It has been contended that lung cancer is routinely overdiagnosed as a cause of death on death certificates, thus undermining the study's credibility. But the resultant misclassification of cause of death would presumably be nondifferential, and thus bias results toward the null. To cause overestimation of the association, a greater proportion of women in the spousal smoking groups than in the nonsmoking group would have to be falsely diagnosed as having lung cancer. Because the study

cohort was made up of *nonsmoking* women, there would be little reason for such a pattern (unless, of course, all such cases came from women who falsely reported their initial smoking status or took up smoking in the course of the study *and* the misclassification/smoking habit concordance hypothesized by Lee were actually strongly at work).

No information is given regarding whether the same interviewers interviewed both husbands and their wives. Thus, interviewers may not have been blind to spousal smoking characteristics of interviewees. This is likely to have been of little importance, however, because the outcome--lung cancer mortality--was measured prospectively, and thus did not occur for some time *after* exposure had been assessed. If information bias was to some extent operant in the interview, the most likely scenario would find women whose husbands smoked being probed more strongly for admission of their own smoking than were women whose husbands did not smoke. This would tend to *reduce* underreporting of active smoking in the "exposed" group relative to the "unexposed" group. The result would be to *lower* the observed association between husbands' smoking and lung cancer mortality.

Hirayama's cohort includes only married, reportedly nonsmoking women who were at least 40 years of age and "healthy" at the start of the study. In addition, almost all of these women were under 70 years of age, and agricultural families composed a larger part of the cohort than of the general population. Thus, the cohort does not present a proportionately accurate cross-section of the Japanese population as a whole. Nevertheless, there is little obvious reason why a relationship between spousal smoking and lung cancer mortality found in this cohort should be dismissed on the grounds that it is not generalizable to the greater Japanese (or other) population.

The possibility that confounding by other risk factors explains an observed association must be considered in any study. For lung cancer, of course, smoking, gender, and age are major risk determinants. Restriction of comparison groups to same-gender nonsmokers avoids possible effects due to gender or smoking (but see misclassification discussion regarding smoking status). Age is only partially restricted in the study design, so its consideration in the analysis is essential. Hirayama chose to control for husband's age in analyzing the cohort study's results. All observed associations persisted after such adjustment. Spousal ages *should* be closely correlated, but direct adjustment using the subject's own age rather than the age of their spouse would clearly be preferable. One such analysis *was* supplied (Hirayama, 1983a), and in it a significant association between spousal smoking and lung cancer mortality persisted. Furthermore, in analyzing the nested case-control studies, adjustment for wife's age was used throughout, which produced findings that confirmed the results of the cohort study.

The potential role of confounding by other factors in the observed results has received considerable emphasis. A correlation between smoking and lower socioeconomic status with concomitant lifestyle and environmental differences could be expected. Among these differences, particular attention has been paid to the possible effect of dietary factors (particularly low beta-carotene intake) and occupational exposures, both of which, some hold, should correlate with spousal smoking and thus could bring about the observed association even if spousal smoking and ETS exposure have no effect. Yet, neither stratification on daily green-yellow vegetable consumption--the best available surrogate for beta carotene intake in the data--nor on agricultural versus nonagricultural occupation of husband eliminated the association between spousal smoking and lung cancer mortality in the cohort study. Similarly, adjustment for husband's occupation and any of five dietary habit characteristics, along with wife's age, yielded similar results in the case-control approach. Thus, neither of the major proposed confounders satisfactorily accounts for the observed results.

Because the data set does not contain the necessary information to examine effects due to differences in cooking practices (such as stir-frying), this cannot be ruled out, although such practices might be expected to co-vary with some of the dietary factors considered in the analyses. Similarly, use of coal for cooking or heating cannot be directly assessed, although a degree of covariance with dietary habits or occupation is likely.

Husbands' drinking habits were only marginally associated with lung cancer risk; mortality rates stratified by both drinking and smoking would have been more useful (and stratification by wives' own drinking habits would have been more useful still).

When lung cancer mortality among wives is stratified by wife's age (in 10-year increments) and husband's smoking category, a clear dose-response pattern is seen only in the 40 to 49 and 50 to 59 age strata, whereas a decrease in mortality with spousal smoking is seen in the 70 and older stratum. Given that the latter stratum includes less than 1% of the cohort and very few deaths, its rates are too unstable to justify much confidence. The dose-response pattern does become weaker with ascending age strata, however, which has led to conclusions of inconsistency with an ETS-lung cancer connection and presence of confounding. Hirayama has proposed that age-related increases in spousal mortality, smoking cessation, and decreased time spent in husband's proximity during the followup period may account for the observed pattern (Hirayama, 1990a). The proximity effect seems questionable because retirement of older husbands would eliminate time spent away from the house at work, but the other arguments are plausible. Alternatively, older women recently married to smokers may be more likely to die from competing causes of death that increase with age before passive-smoke cancer develops. Remarriage, possibly to a spouse whose smoking habits differ from those of the former spouse,

also would increase with age and could lead to misclassification of (former) exposure with a bias toward the null. (It is unfortunate that history of former spouses' smoking habits and recency of marriage apparently were not obtained in the baseline interview because if the information had been collected, the aforementioned problems could have been readily addressed.) Temporal trends in some risk modifiers, such as dietary factors, also could play a role.

Confounding cannot be ruled out entirely in certain instances, but the underlying question that must be raised in this regard is the following: *If* the spousal smoking group contains a disproportionate number of individuals with risk-elevating factors such as poor diet, lack of exercise, low socioeconomic status, and occupational hazard exposure, and these factors are sufficient to produce an increase in lung cancer mortality relative to the spousal nonsmoking group, despite an absence of any real smoking effect, *why* does this multitude of risk factors result in elevations of established smoking-related diseases only and no substantial elevation of risk of other causes of mortality (except brain cancer, which encompasses relatively few deaths)?

In considering the study's results in broader terms, Hirayama's findings are consistent with the hypothesis that exposure of nonsmoking women to passive smoke via spousal smoking increases risk of lung cancer. The observed association is statistically significant. In addition, the persistence of the association after stratification on numerous variables, the observation of a parallel association in nonsmoking husbands of smoking wives, the appearance of associations with other smoking-related diseases, the existence of a dose-response pattern in most analyses of strata containing adequate numbers, and the production of similar conclusions by either cohort or case-control approaches argues against attribution of results purely to chance or confounding.

Possible inclusion of active smokers among "nonsmoking" spouses of smokers through misclassification bias or differential change in smoking status during followup remains the study's greatest weakness. This problem could have been addressed by followup interviews or questionnaires coupled with verification of smoking status by alternative means in a subsample of the cohort, and still could be. In addition, losses to followup and failure to use more sophisticated survival analysis techniques are weaknesses that probably reduced the study's power.

Overall, the Hirayama study provides supportive, although not definitive, evidence that ETS exposure increases lung cancer risk.

A.4.13. HOLE(Coh) (Tier 1)

This prospective cohort study was undertaken in the towns of Paisley and Renfrew, Scotland. The primary objective was to explore the relationship between passive smoking and cardiorespiratory symptoms and mortality, including lung cancer. The towns were selected

because they are situated in an area with a high incidence of lung cancer. All persons residing in these towns between 45 and 64 years of age, inclusive, were visited between 1972 and 1976. Each person was asked to complete a self-administered questionnaire and to visit a cardiorespiratory screening center where further interviews were conducted; 80% (15,399 persons) responded.

Participating households in which at least two "apparently healthy" subjects lived were included in the study, yielding a study population of 3,960 males and 4,037 females. Data on smoking habits were obtained from the questionnaire and verified by interview at the screening visit. Mortality among subjects was traced using the Scottish National Health Service Central Register and General Register offices (for death certificate linkage), as well as the national cancer registry system. Results for followup through 1982 were published in 1984 (Gillis et al., 1984). The primary results reported here are for followup through 1985, published in 1989 (Hole et al., 1989). In addition, the results of unpublished data extending followup through December of 1988 are reported (personal communication from Hole to A.J. Wells).

Smoking habits were divided into three categories: persons who have never smoked, former smokers, and current smokers. In addition, the number of cigarettes smoked per day was obtained for current smokers. Both pipe and cigar smokers were excluded from the group who had never smoked. Never-smokers with former or current smokers as cohabitants in their household were classified as passive smokers; otherwise never-smokers were classified as "controls." This classification yielded 1,538 passive smokers and 917 controls for both sexes combined. The corresponding numbers for females alone are 1,295 and 489.

The number of lung cancer deaths among females occurring in the cohort during the followup period is only six, too small to yield much statistical precision. The unpublished data extending followup through 1988 includes one additional female lung cancer death that occurred subsequent to 1985. The crude relative risk is 2.27 (95% C.I. = 0.40, 12.7), which is in the direction of a positive association between ETS exposure and lung cancer. The extremely wide confidence interval is the result of the small number of cancer deaths being compared and indicates that the data could easily arise when the true value of the relative risk is much larger or smaller than the estimated value. After adjustment for age and social class, the relative risk is 1.99 (95% C.I. = 0.24, 16.72). Lung cancer incidence was somewhat higher than mortality (10 cases vs. 7 deaths), yielding an adjusted relative risk of 1.39 (95% C.I. = 0.29, 6.61). The relative risks for adjusted mortality (5.30) and incidence (3.54) were higher in males than in females but were based on even fewer cases (four deaths, six incident cases).

Although the observed association could easily occur by chance, it is a useful contribution to the pool of evidence on lung cancer and passive smoking. Consequently, it is worth noting that the observed associations are not likely to be attributable to other factors, because they persisted

after control not only for age and gender, but for social class, diastolic blood pressure, serum cholesterol, and body mass index. Thus, differences in lifestyle or environmental factors such as diet, housing, and employment between passive-smoking households and nonsmoking households is an unlikely source of the results. Specific adjustment for potential occupational exposures or radon were not carried out, but these variables would presumably co-vary with social class to a great extent.

As for other sources of bias, interviewer bias can be discounted because subjects were "apparently healthy" at interview and supplied smoking information before cardiovascular screening, and the investigators did not begin determining the passive smoking status of subjects until 1983 (for the first published study on this cohort). The extent of loss to followup is not specified, so one cannot tell whether this was a potential source of problems. However, linkage was carried out through two registries for general mortality and an additional registry specifically designed for cancers. Diagnoses of cancer mortality from death certificates were checked against cancer registry records for verification, thus reducing potential inaccuracies attendant on use of death certificates.

Some data regarding misclassification were collected in an additional questionnaire administered to a portion of the cohort at some unspecified point in the study. Among controls, 5% said that their household contained a smoker--presumably someone who had not met the inclusion criteria (e.g., age 45 to 64) for the study. Thus, a small portion of the control group was actually currently exposed, which would produce a slight bias toward the null. Differential misclassification of smokers as never-smokers resulting from concordance of smoking habits among cohabitants cannot be assessed or ruled out, despite the authors' suggestion that persons cohabitating with smokers may be more likely to falsely claim to be smokers themselves, providing a bias toward the null.

In summary, this study appears well designed and executed, but the number of ETS-exposed subjects is small. Although the study carries little statistical weight, there are no apparent methodological problems that would limit its usefulness otherwise.

A.4.14. HUMB (Tier 2)

A.4.14.1. *Author's Abstract*

"As part of a population-based case-control study of lung cancer in New Mexico, we have collected data on spouses' tobacco-smoking habits and on-the-job exposure to asbestos. The present analyses include 609 cases and 781 controls with known passive and personal smoking status, of whom 28 were lifelong nonsmokers with lung cancer. While no effect of spouse

cigarette smoking was found among current or former smokers, never smokers married to smokers had about a twofold increased risk of lung cancer. Lung cancer risk in never-smokers also increased with duration of exposure to a smoking spouse, but not with increasing number of cigarettes smoked per day by the spouse. Our findings are consistent with previous reports of elevated risk for lung cancer among never-smokers living with a spouse who smokes cigarettes."

A.4.14.2. *Study Description*

This population-based case-control study was conducted through the New Mexico Tumor Registry during 1980-84. The original purpose was to explain differing lung cancer occurrence in Hispanic and non-Hispanic whites in New Mexico. The study questionnaire included questions on spousal smoking and on indirect exposure to asbestos through a spouse's job. The current report describes the risks associated with those exposures in smokers and nonsmokers. The data on ETS exposure in nonsmokers is extracted from the larger study containing smokers.

For the whole study, a total of 724 eligible primary lung cancer patients were identified, of which 641 were interviewed (89%). About one-half (48%) of the case interviews were conducted with the subject. Information on the remaining subjects was obtained from surrogates, generally the surviving spouse or a child. Cases were collected in two series, the first consisting of patients with cancer incident in 1980-82. That group includes all cases less than 50 years of age and all Hispanics, but not those exclusively. The number of cases was supplemented by a second series of patients with cancer incident to a 1-year period beginning November 1983. Most of the controls were selected by random telephone sampling, but some older subjects were randomly selected from Medicare participants. The control group was frequency-matched to the cases for sex, ethnicity, and 10-year age category, at a ratio of approximately 1.2 controls per case. Interviews were held for 784 of the 944 eligible controls, with 98% of the responses from subjects.

The term "never-smoker" means not a cigarette smoker, where the latter is defined to be someone who has smoked for at least 6 months. The smoker classification is divided further into current smokers and ex-smokers. The current smoker status includes smokers who have stopped within 18 months before the interview; the ex-smoker status applies if smoking ceased more than 18 months before the interview. Assuming that the minimum 6-month duration of smoking is intended to apply to current and ex-smokers, never-smokers could have smoked previously for up to 6 months.

An ETS-exposed subject is one ever-married to a spouse who smoked cigarettes, regardless of the spouse's use of pipes or cigars. No information was obtained on exposure to ETS from other sources, such as from other household smokers, in the workplace, or from parental

smoking during childhood. Measures of ETS exposure from spousal smoking include duration of exposure (in years) and the average number of cigarettes smoked per day by the spouse. The ETS subjects (never-smokers) include 20 (4) female (male) cases and 162 (130) controls (the article reports 8 male cases, the number used in much of the analyses, but 4 of those 8 were found to be smokers, personal communication from Humble). The age distribution for the female cases (controls) is as follows: age less than 65, 5 (74); age 65 or more, 15 (88).

The odds ratio for the crude data on female never-smokers is 1.8 (90% C.I. = 0.6, 5.4) for spousal smoking of cigarettes only and 2.3 (90% C.I. = 0.9, 6.6) when spousal smoking also includes use of pipes and cigars. Based on mean cigarettes per day smoked by the spouse, the odds ratio of 1.2 at more than 20 cigarettes per day is somewhat lower than the odds ratio of 1.8 at the lower rate, fewer than 20 cigarettes per day. For duration of exposure, the odds ratio increases from 1.6 at less than 27 years to 2.1 at 27 or more years. It is reported that adjustment for age and ethnicity did not alter these results from the crude analysis. A trend test is included for duration of spousal smoking, but the sample sizes are too small to be meaningful. Application of logistic regression to adjust for variables gives values very close to the odds ratios for the crude analyses shown above for spousal smoking, for use of cigarettes only and also for combined use of cigarettes, cigars, and pipes.

The distribution of cases by cell type is given, but only with males and females combined. The ratios of ETS-exposed cases to the total, by cell type, are as follows: squamous cell (2/4), small cell (1/1), adenocarcinoma (either 6/12, 7/12, or 8/12), and others (either 3/3, 2/3, or 1/3, depending on correct ratio for adenocarcinoma).

The authors conclude that the results indicate increased risk from ETS exposure in never-smokers but not in active smokers.

A.4.14.3. *Comments*

This study evaluates smokers as well as nonsmokers for increased risk of lung cancer from spousal smoking. Not surprisingly, the number of smokers among the cases far outweighs the number of nonsmokers. No evidence of added risk to smokers from passive smoking is found. Such an evaluation, however, puts a great deal of faith in the exposure data and the power of statistical methods to detect what may be only a marginal increase in risk from ETS on top of active smoking.

Of more central concern to this review is the assessment of lung cancer from ETS exposure in never-smokers. The ETS data are taken from a larger study, so the matching no longer applies, although the adjustment for those variables (ethnicity and age category) in the analysis is

worthwhile. The article suggests that the high rate of proxy response for cases in the original study (52%) may be due, at least in part, to inclusion of decedent cases. That topic is not explicitly addressed, however, and controls were not matched to cases on vital status. Never-smokers apparently may have a history of smoking, provided it is of less than 6 months' duration. Whether any never-smokers actually have a short smoking history is not discussed, but the never-smoker classification is less strict than in most studies.

The data are evaluated in a number of different ways, consistently yielding an increased odds ratio. The number of cases, however, is too small (15 exposed, 5 unexposed) for the observed odds ratio to achieve statistical significance. Similar values of the odds ratios might be observed in a larger study, but, of course, that cannot be assumed. The study outcome is consistent with an association between ETS exposure and lung cancer occurrence.

A.4.15. INOU (Tier 4)

A.4.15.1. *Author's Abstract*

(*Note:* No abstract was provided; the following was paraphrased from author's discussion.)

A case-control study on smoking and lung cancer in women was conducted in Kamakura and Miura, both in Kanagawa prefecture, Japan. The two cities are distinctly different in social environment; the former is a residential community and the latter is a fishing village. After stratification on city and age groups, the odds ratio of lung cancer in nonsmoking wives was shown to be 1.58 when husbands smoked fewer than 19 cigarettes a day and 3.09 when husbands smoked 20 or more cigarettes a day. For comparison, the odds ratio for active smoking is 5.50. Although the study size is quite small, it provides additional evidence favoring the passive smoking and lung cancer hypothesis.

A.4.15.2. *Study Description*

This study was conducted to assess the roles of active and passive smoking in the etiology of lung cancer in women. It is unclear how subjects or diagnoses were obtained, but cases are women who died of lung cancer in Kamakura or Miura in the time periods 1980-83 and 1973-81, respectively. Controls, consisting of women who died of cerebrovascular disease during the same timeframes, are individually matched to cases on year of birth, year of death (± 2.5 years), and district of residence. It is not clear whether incident cases were used.

Face-to-face interviews were conducted by public health nurses and midwives. ETS subjects consist of the 28 nonsmoking cases and 62 nonsmoking controls remaining after elimination of 9 cases and 12 controls who were smokers. Husband's smoking status was not

available for unspecified reasons in a total of 8 cases and 20 controls, but these figures include smokers as well as nonsmokers. The exact number of nonsmokers for which spousal smoking status was available is not specified but can be back-calculated from what is given (see below). No information is given on the number of proxy respondents, the age distribution of the subjects, or attempts to confirm diagnoses of primary lung cancer.

The term "nonsmoker" is not defined, so it is not clear whether it refers to persons who never smoked or who do not smoke at present. Nonsmoking women whose husbands smoke at least five cigarettes per day are classified as exposed to passive smoking. Considerations of former smoking or marital status, ETS exposure at the workplace or in childhood, and duration of exposure are not addressed. No attempts to verify the reliability or validity of the data are mentioned.

The number of subjects is not delineated by case versus control and exposed versus unexposed figures. They can be determined from the odds ratio and confidence interval, however, as 18 of 22 (exposed over total) cases and 30 of 47 controls. For nonsmoking women with smoking husbands, the crude odds ratio calculated by the reviewers is 2.55 (95% C.I. = 0.74, 8.78). (*Note*: OR = 2.25 is erroneously reported in the article. The OR value of 2.55 has been confirmed by Hirayama.) When husbands' smoking is divided into two strata (< 19 cig./day and 20+ cig./day), the odds ratios increase with exposure from 1.16 to 3.35, giving a statistically significant trend ($p < 0.05$). Age-adjusted odds ratios of 1.39 and 3.16 are reported for the two strata; adjustment for both age and district yields corresponding odds ratios of 1.58 and 3.09. (*Note:* The first OR value, 1.58, is incorrectly reported in the article as 2.58. The value 1.58 has been confirmed by Hirayama.) The authors conclude that, although the study size is quite small, the results provide more evidence favoring the hypothesis that passive smoking causes lung cancer.

A.4.15.3. *Comments*

The number of subjects remaining after active smoking and missing data exclusions is small, guaranteeing poor power and lack of statistical significance in the absence of large odds ratios. The details on study design are limited. The source of cases and controls is not mentioned, for example, and it is unclear whether incident or prevalent cases were used.

Information regarding quality control and related concerns is equally sparse. Interviewers used standardized questionnaires, which would help to promote consistency, but no mention is made of blinding them to subject background or study question, the absence of which could introduce interviewer bias (probably in a positive direction). Because cases and controls are stated to have died during the study period, it is probable that proxy respondents were required, but the

extent is unknown. In addition, neither duration of ETS exposure from spousal smoking nor exposure from other sources, such as other cohabitants, was considered. The resultant inaccuracy of exposure assessment probably biases the results toward the null. Lack of information on former smoking status or verification of diagnosis may introduce biases of indeterminate direction. Except insofar as the district acts as a surrogate for factors related to socioeconomic status, no risk modifiers other than age or district of residence were considered. The meaning of "nonsmoker" is not given, so treatment of smoking history is unknown, and it is unclear whether the accurate and meaningful segregation of never-smoking subjects needed for effective analysis was accomplished.

Although a substantial odds ratio was observed for husband's smoking, these results are based on a small sample with too few details provided to assess adequately the study's design and execution and its bearing on the evidence, particularly with regard to potential sources of bias. The statistical uncertainty of the odds ratios given is reflected in the extremely wide confidence intervals shown. The test for trend does not add any additional information. It is basically a restatement of the significant comparison between the heavily exposed group (husband smokes > 20 cig./day) and the unexposed group. Unfortunately, the brevity of the description of this study in the source available severely limits its utility.

A.4.16. JANE (Tier 2)

A.4.16.1. *Author's Abstract*

"The relation between passive smoking and lung cancer is of great public health importance. Some previous studies have suggested that exposure to environmental tobacco smoke in the household can cause lung cancer, but others have found no effect. Smoking by the spouse has been the most commonly used measure of this exposure.

In order to determine whether lung cancer is associated with exposure to tobacco smoke within the household, we conducted a population-based case-control study of 191 patients with histologically confirmed primary lung cancer who had never smoked and an equal number of persons without lung cancer who had never smoked. Lifetime residential histories including information on exposure to environmental tobacco smoke were compiled and analyzed. Exposure was measured in terms of 'smoker-years,' determined by multiplying the number of years in each residence by the number of smokers in the household."

A.4.16.2. ***Study Description***

This study was undertaken in New York State to clarify the role of exposure to tobacco smoke in the household as a possible cause of lung cancer among nonsmokers. Interviews were conducted with former smokers as well as never-smokers initially (Varela, 1987), but because matching was carried out on smoking status, only never-smoking case-control pairs were included in the analyses for this article. The study includes both males and females, which are combined in all of the analyses. There are 146 (45) female (male) pairs.

Cases are never-smokers aged 20 to 80 years newly diagnosed with lung cancer at 125 referral centers in New York from July 1, 1982, to December 31, 1984. Controls are cumulatively sampled never-smokers identified from files of the New York Department of Motor Vehicles. Controls are individually matched to cases on age (± 5 years), gender, and residence. In addition, the same interview type (proxy or direct) was used for controls as for their corresponding cases. Exposure data were collected face-to-face via standardized questionnaire, and interviewers were apparently uninformed of the subject's diagnosis.

From the 439 case-control pairs interviewed, 242 pairs containing former smokers and 6 pairs with a mismatch on the source of response were excluded. Of the remaining 191 pairs used in the ETS study, interviews were conducted directly with the subjects in 129 pairs (68%) and with proxies in 62 pairs (32%) (if a proxy was interviewed for a case, then a proxy was used for the matching control as well). No demographic comparisons were provided for the ETS cases and controls. For the whole study including smokers, the mean age of cases and controls is nearly identical (67.0 and 68.1, respectively; Varela, 1987). Histological verification of diagnosis was obtained for all but five cases (for whom only clinical information was available) out of the initial population of 439.

Persons smoking no more than 100 cigarettes over the course of their lifetime qualified as never-smokers for this study. Cigar or pipe smoking was apparently not considered. Exposure to ETS was deemed to occur when a smoker lived in the subject's household at any time from infancy to adulthood. Both total household smoke exposure and spousal smoke exposure were determined. Preadult (before 21 years of age) and adult exposure were examined separately. Exposures were computed in units of "smoker-years," the total number of years lived with each smoker summed over smokers. In addition, pack-years were calculated for spousal smoking. Workplace exposure also was estimated by smoker-years, whereas exposure in social settings was estimated subjectively on a scale from 1 to 12 for each decade of life and summed. Exposure data were not checked, and marital status was not considered in the analyses. No information on tumor type or location was provided for the never-smoking population.

Preadult exposure to 24 or more smoker-years occurred in 52 (29) cases (controls), whereas 82 (94) were exposed to 1 to 24 smoker-years and 57 (68) were unexposed. Odds ratios were calculated using matched-pairs regression analysis. Preadult passive smoking yielded increasing odds ratio of 1.09 (95% C.I. = 0.68, 1.73) for 1 to 24 smoker-years and 2.07 (1.16, 3.68) for 25 or more smoker-years. The odds ratios for adult exposure are low but also increase--from 0.64 (0.34, 1.21) at 1 to 24 smoker-years to 1.11 (0.56, 2.20) at 75 or more smoker years. The odds ratios for lifetime exposure increase from 0.78 (0.36, 1.67) at 1 to 24 smoker-years to 1.80 (0.83, 3.90) at 25 to 99 smoker-years and then dip to 1.13 (0.56, 2.28) at 100 or more smoker-years. Spousal smoking was not significantly associated with lung cancer. In fact, when results were stratified by type of interview, proxy interviews yielded strong and, in some instances, statistically significant negative associations for spousal smoking, with odds ratios between 0.20 and 0.68 for ETS expressed in terms of present or absent, smoker-years, and pack-years of exposure. The odds ratios for direct interviews, in contrast, range from 0.71 to 1.10 and are uniformly higher than the odds ratios for corresponding proxy responses. Workplace exposure to 150 or more person-years yielded an odds ratio of 0.91 (0.80, 1.04), whereas a social setting exposure score of 20 led to a statistically significant *decreased* odds ratio of 0.59 (0.43, 0.81).

The authors conclude that they found a significant adverse effect of relatively high levels of exposure to ETS during early life (before age 21). For those who were exposed to 25 or more smoker-years in their first two decades of life, the risk of lung cancer doubled. By contrast, the authors found no adverse effect of exposure to ETS during adulthood, including exposure to a spouse who smoked. This lends further support to the observation that passive smoking may increase the risk of subsequent lung cancer, and it suggests that it may be particularly important to protect children and adolescents from this environmental hazard.

A.4.16.3. *Comments*

The number of never-smoking cases is relatively large, resulting in above-average statistical power for evaluation of ETS effects. Controls were matched to cases on smoking status, as well as the key demographic factors of age, gender, and neighborhood. Comparability of cases and controls was likely good, as evidenced by the similar mean ages for the total population, although no other comparative information is available. In view of the use of population-based, basically healthy controls, it is questionable that any attempted diagnostic blinding would be effective. The study's matching on smoking status with subsequent retention of matching and use of matched-pairs analysis for ETS exposure effectively eliminates potential effects on risk attributable to age, gender, or residence, and it makes bias by related factors (such as

socioeconomic status) less likely. A rare feature is the use of matching on interview type (i.e., proxy or subject direct) to control for bias due to this source. Comparison of spousal smoking results for direct and proxy interviews, however, indicates consistently lower estimated risks from proxies. This suggests that use of proxy respondents did not merely lead to increased random misclassification but might have biased the outcome toward a negative association. The authors posit that proxies of lung cancer patients may be more likely to underreport exposure than those of control subjects. Curiously, however, although the authors report that odds ratios "frequently differed according to type of interview," they do not specify how the odds ratios differed for exposure other than spousal smoking. Also, the composition of the proxy groups--relative proportions of spouses, other relatives, and friends or associates--is never discussed, leaving unexplored the possibility that misreporting by spouses of cases may lie at the heart of the observed discrepancy. It is also interesting that the outcome of self-responses versus proxy responses in this study is in the opposite direction of the findings in GARF. Diagnostic misclassification is unlikely, given the histological verification of nearly all cases.

The restriction of subjects to persons smoking no more than 100 cigarettes in their lifetime theoretically eliminates active smoking as a source of bias, although no verification of smoking status was undertaken. Consideration of potential sources of ETS exposure is commendably thorough, and the calculation of total years of living with smokers, regardless of relation to the smoker, as an index of household smoke exposure minimizes the possibility that any source (e.g., roommates) is overlooked. In contrast, the index of exposure in social settings is highly subjective, and persons more habituated to passive smoke may report a given exposure as less severe than persons less accustomed to smoke, thus creating a negative bias. The proportion of controls classified as exposed to ETS is 80%, which is high in comparison with other studies. This suggests that some exposed controls may have only minor exposure to ETS, making detection of an association (if present) less likely. Unlike almost every other ETS study, males and females are combined in the analysis and only the joint results are reported. Because there are 45 (146) pairs of males (females), the sample sizes are sufficient to warrant reporting odds ratios separately by sex and to test the hypothesis of no difference due to gender.

Lung cancer odds ratios for adulthood, lifetime, and spousal smoking are consistently well below 1 for low ETS exposure relative to nonexposure, as if exposure had a protective effect. Thereafter, however, the odds ratios associated with increasing levels of exposure are suggestive of an upward trend in response. Although we would not dismiss the occurrence of this outcome as attributable to chance alone, it is consistent with the baseline lung cancer mortality rate in the control population simply being higher than that of the case population for reasons other than exposure to spousal smoking. A pervasive (systematic) negative bias linked with exposure could

also produce such an effect. Both of these contingencies are necessarily speculative because there is no evidence in the article to support either, aside from the outcome of the data analysis. Further fueling the speculation, however, are the markedly lower odds ratios obtained from surrogate responses, indicative of some source of bias acting unequally on proxy and nonproxy sources. Also speculative is the idea that using predicted responses from a model that fits the data poorly might produce such an effect, but that level of detail is beyond the scope of most published articles, including this one. Some discussion of these issues by the authors, as well as *separation of the analyses by sex*, would enhance interpretation of results and facilitate their comparison with results of other studies on females.

The authors' finding that exposure during childhood and adolescence appears to influence subsequent lung cancer risk more than exposure during adulthood raises some interesting possibilities. More time may be spent in proximity to a household smoker (particularly the mother), on average, in childhood than in adulthood. According to data presented by K.M. Cummings (Roswell Park Memorial Institute, Buffalo, New York) at the Science Advisory Board meeting on EPA's draft ETS report (U.S. EPA, 1990), on December 4-5, 1990, heavy childhood exposure is a better surrogate for total lifetime exposure than is spousal exposure. Also, early exposure may appear to become a risk, either due to a long latency period for lung cancer or, perhaps, due to increased susceptibility at an earlier age. The results suggesting an effect from early exposure but not from spousal smoking are more nearly atypical than reinforced by other studies, though, and the number of exposure sources considered raises the possibility that the strength of association seen for preadult exposure may be due to chance. However, after elimination of 78 pairs with incomplete marriage or household exposure data, the association persisted and was strengthened (OR = 2.59), arguing against chance as the major influence. It is unclear what role, if any, negative bias due to proxy respondents may have had in the nonspousal analyses.

In summary, the findings for preadult exposure are not readily attributable to chance or confounding, although some role of interviewer bias or other factors such as diet cannot be ruled out. No association with lung cancer incidence is observed for spousal smoking. The authors conclude, however, that, spousal smoking aside, other sources of household ETS exposure support the conclusion that exposure to ETS can cause cancer. That conclusion is not unequivocal in our view. In general, the odds ratios (aside from preadulthood exposure) tend to be low but trend upward with exposure, exhibiting more of a patterned response than one might expect to see due to randomness. This is puzzling because there is no apparent source of bias and the study appears to have been conducted with considerable forethought and thoroughness. The only exception

noted is the lack of separate analyses and comparisons of males and females. These concerns notwithstanding, the study is a useful addition to the literature on ETS exposure and lung cancer.

A.4.17. KABA (Tier 2)

A.4.17.1. *Author's Abstract*

"Among 2,668 patients with newly diagnosed lung cancer interviewed between 1971 and 1980, 134 cases occurred in 'validated' nonsmokers. The proportion of nonsmokers among all cases was 1.9% (37 of 1,919) for men and 13.0% (97 of 749) for women, giving a sex ratio of 1:2.6. Kreyberg Type II (mainly adenocarcinoma) was more common among nonsmoking cases, especially women, than among all lung cancer cases. Comparison of cases with equal numbers of age-, sex-, race-, and hospital-matched nonsmoking controls showed no differences by religion, proportion of foreign-born, marital status, residence (urban/rural), alcohol consumption, or Quetelet's index. Male cases tended to have higher proportions of professionals and to be more educated than controls. No differences in occupation or occupational exposure were seen in men. Among women, cases were more likely than controls to have worked in a textile-related job (RR = 3.10, 95% C.I. = 1.11, 8.64), but significance of this finding is not clear. Preliminary data on exposure to passive inhalation of tobacco smoke, available for a subset of cases and controls, showed no differences except for more frequent exposure among male cases than controls to sidestream tobacco smoke at work. The need for more complete information on exposure to secondhand tobacco smoke is discussed."

A.4.17.2. *Study Description*

In 1969, the American Health Foundation began interviewing newly diagnosed lung cancer patients with cancer at sites potentially related to tobacco use for a case-control study (Wynder and Stellman, 1977) that is still ongoing. The current article considers the data on lung cancer in nonsmokers alone collected from newly diagnosed lung cancer patients between 1971 and 1980. Several factors are of interest: histology, demographic factors, residence, Quetelet's index, alcohol consumption, previous diseases, occupation and occupational exposures, and ETS exposure. The number of nonsmokers among the cases is small, so the authors consider the results to be preliminary.

The study from which the data on lung cancers in nonsmokers are extracted is a very large effort that includes tobacco-related cancers at multiple organ sites and includes smokers as well as nonsmokers. The cases are from approximately 20 hospitals in 8 U.S. cities (about one-third from New York City). With reference to the lung cancer cases in that study, histologic type of lung

cancer was determined from pathology reports and discharge summaries. Secondary lung cancer cases were excluded. Controls consist of hospital patients with diseases unrelated to tobacco use who were pair-matched with cases on hospital, age (within 5 years), sex, race (with five exceptions), date of interview (within 2 years), and nonsmoking status. Cases appear to be incident, and control sampling is density. All subjects were interviewed while they were in the hospital. The questionnaire for the interviews was expanded in 1976. Questions on exposure to ETS were not included, however, until an addendum to the questionnaire in 1978, which was then modified in 1979.

The term "nonsmoker" applies to subjects who have smoked fewer than one cigarette, pipe, or cigar per day for a year. The term "never-smoker" is used interchangeably. Independent of the intended definition, however, subjects whose hospital charts indicated any record of smoking, even in the remote past, were excluded from the nonsmoker classification. ETS subjects include 53 (25) females (males), after combined attrition of 22 (9 without primary lung cancer and 13 with a record of smoking). The age distribution of the female cases (controls) is as follows: age less than 50, 12 (15); age 50 to 59, 26 (24); age 60 to 69, 29 (34); age 70 or more, 30 (24). Histologic data on lung cancer type are given for female cases: squamous cell (16), adenocarcinoma (60), alveolar (12), large cell (4), and unspecified (5). The authors report that exposed cases did not differ from the unexposed cases in the distribution of histologic type.

A person is "ETS exposed" (1) at home, if currently exposed on a regular basis to family members who smoke, (2) at work, if currently exposed on a regular basis to tobacco smoke at work, and (3) to spousal smoke, if the spouse smokes. There are data on 53 cases and their controls for exposure at home and at work, but data on only 24 cases and 25 controls for spousal smoking. This is because of the change in the questionnaire from 1978 to 1979 and because spousal smoking was only applicable for women currently married. Because nonsmoking status was a variable for matching, the 53 pairs of cases and controls for analysis of exposure at home or at work are matched; the data for spousal smoking, however, are technically not matched. There is no indication at all of an association between ETS exposure and lung cancer for women from exposure at home, at work, or from spousal smoking. For ETS exposure at home, there are 16 of 53 (exposed/total) cases and 17 of 53 controls; for exposure at work, the figures are 26 of 53 cases and 31 of 53 controls; and for spousal smoking, the data are 13 of 24 cases and 15 of 25 controls. No statistical calculations are provided for females. From our calculations, the odds ratio for spousal smoking is 0.79 (95% C.I. = 0.25, 2.45). (Among male subjects, exposure to ETS in the workplace was slightly significant, $p = 0.05$, as reported in the article.) For other potential risk factors for lung cancer in women other than passive smoking, it was found that cases were more likely than controls to have worked in a textile-related job (OR = 3.1; 95% C.I. = 1.1, 8.6), but

the significance of the finding was not clear. It also was found that more female cases had a history of pneumonia compared with controls, but no interpretation could be attached to the observation.

A.4.17.3. *Addendum*

Unpublished preliminary results of a study of ETS and lung cancer in never-smokers conducted at the American Health Foundation have been reported at two meetings--The American Public Health Association (APHA) 119th Annual Meeting, Atlanta, Georgia, November 10-14, 1991, and The Toxicology Forum, 1990 Annual Winter Meeting, Washington, D.C., February 19-21, 1990. A completed report for our review was not available at the cutoff date for inclusion in this document (personal communication with the first author, Dr. G.C. Kabat). Enclosed below is the abstract for the APHA meeting.

RISK FACTORS FOR LUNG CANCER IN LIFETIME NONSMOKERS

Geoffrey C. Kabat, Ernst L. Wynder

Risk factors for lung cancer in lifetime nonsmokers (NS) were assessed in a hospital-based case-control study carried out between 1983 and 1990. The study population consisted of 41 male and 69 female NS cases and 117 male and 187 female NS controls matched on age, race, hospital, and date of interview. Evidence of an effect of exposure to ETS was inconsistent. In males, there was no difference between cases and controls in reported exposure to ETS (yes/no) in childhood, in nonsignificant association with exposure in childhood (OR = 1.6, 95% C.I. = 0.9, 2.8), but no association with exposure in adulthood at home or at work. Male cases were somewhat more likely to have a smoking spouse (OR = 1.6, 95% C.I. = 0.7, 3.9), whereas there was no difference in females. Cases and controls did not differ in reporting a history of previous respiratory diseases. Female cases were more likely to report a history of radiation treatment (OR = 4.3, 95% C.I. = 1.5, 12.3). In females, but not in males, a significant inverse association was observed between body mass index (based on self-reported weight 5 years prior to diagnosis) and lung cancer risk.

A.4.17.4. *Comments*

Although the study contains more than 2,600 patients, only a small number of nonsmokers are available because questions about ETS exposure were not included in the interview until 1978 and the questions were changed in 1979. It is not known just how the questionnaire was changed,

although the general tenor of the article suggests care in study planning and execution. The design for the larger study from which the ETS data are taken is pair-matched on numerous factors of potential interest, including "nonsmoking status," which contributes favorably to the analysis of ETS data alone. Cases with secondary tumors were excluded, histological type was considered, and all subjects were personally interviewed. It appears that only the currently married females were included in the question regarding exposure to spousal smoke, which alleviates the need to make some approximating assumptions regarding exposure of widows, single females, and so forth.

Two areas that may need to be addressed in the analysis of ETS subjects have to do with the definition of "ETS exposure" and "nonsmoker." The duration of smoking was comparable in cases and controls, but interview questions regarding exposure to ETS refer only to current exposure (this is not explicit in the article but was confirmed by the first author). Any effect from reliance on current exposure alone should be a bias toward the null hypothesis. Also, a measure of exposure in units (e.g., number of cigarettes per day or pack-years smoked by spouse) would make the question less subjective and help to dichotomize on ETS exposure more sharply. Because lung cancer may have a latency period of 20 years or so, exposure in the past, both in terms of duration and intensity, should be more meaningful than current exposure alone. With regard to the definition of nonsmoker, the requirement is less rigid than is often imposed. Ever-smokers are included provided they did not smoke more than the equivalent of 1 cigarette per day for 1 year (about 18 packs). It is difficult to know, however, what constitutes a "negligible" level of past smoking. Any bias from former smoking should inflate the relative risk, but that outcome appears unlikely in this study (RR = 0.74).

One of the factors of interest to the investigators is occupation, so cases and controls were not matched on that variable. For ETS exposure, occupation could be a confounding factor. Among females, the controls contain a higher percentage of professional and skilled workers than do the cases (47 to 25) and a lower percentage of housewives (41 to 50). Some differences are also apparent in religious preference between cases and controls that may bear some influence through lifestyle or dietary practices. Variables such as these may need to be taken into account in an adjusted analysis when more data become available.

A.4.18. KALA (Tier 1)

A.4.18.1. *Author's Abstract*

"A case-control study was undertaken in Athens to explore the role of passive smoking and diet in lung cancer, by histologic type, in nonsmoking women. Among 160 women with lung

cancer admitted to one of seven major hospitals in Greater Athens between 1987 and 1989, 154 were interviewed in person; of those interviewed, 91 were lifelong nonsmokers. Among 160 identified controls with fractures or other orthopedic conditions, 145 were interviewed in person; of those interviewed 120 were lifelong nonsmokers. Marriage of a nonsmoking woman to a smoker was associated with a relative risk for lung cancer of 2.1 (95% C.I. = 1.1, 4.1); number of cigarettes smoked daily by the husband and years of exposure to husband's smoking were positively, but not significantly, related to lung cancer risk. There was no evidence of any association with exposure to smoking of other household members, and the association with exposure to passive smoking at work was small and not statistically significant. Dietary data collected through a semiquantitative food-frequency questionnaire indicated that high consumption of fruits was inversely related to the risk of lung cancer (the relative risk between extreme quartiles was 0.27 (95% C.I. = 0.10, 0.74). Neither vegetables nor any other food group had an additional protective effect; furthermore, the apparent protective effect of vegetables was not due to carotenoid vitamin A content and was only partly explained in terms of vitamin C. The associations of lung cancer risk with passive smoking and reduced fruit intake were independent. Passive smoking was associated with an increase of the risk of all histologic types of cancer, although the elevation was more modest for adenocarcinoma."

A.4.18.2. *Study Description*

This study was undertaken in Athens, Greece, in 1987-89. It sought to explore the role of passive smoking and diet in the causation of lung cancer in nonsmoking women. All data used in the study were collected specifically for that purpose.

Cases are never-smoking women hospitalized in one of seven Greater Athens area hospitals during an 18-month period of 1987-89 with a definite diagnosis of lung cancer from histologic, cytologic, or bronchoscopic exam. Controls were selected from female never-smoking patients in the orthopedic ward of the same seven hospitals and an orthopedic hospital. A control was interviewed within 1 week of a corresponding case, thus essentially density-sampled but otherwise unmatched. Cases were not specifically restricted to incident cancers. All subjects were interviewed face-to-face by one of five trained interviewers; interviews apparently were unblinded. A total of 160 lung cancer cases and an equal number of controls were initially identified; 6 cases and 12 controls were too ill to interview, whereas 3 controls and no cases refused to participate. After exclusion of smokers, 91 cases and 120 controls remained. The age distributions of the cases and controls are very similar: for cases (controls), 16.5% (14.2%) were less than 50 years of age, 19.8 (18.3%) were 50 to 59, 29.7 (25.8%) were 60 to 69, and 34.1 (41.7%)

were 70 or older. Current residence, level of education, occupation (housewife vs. other) and marital status were also similarly distributed between cases and controls. Case diagnosis was established by histology (48%), cytology (38%), or bronchoscopy (14%), with exclusion of cancers diagnosed as secondary.

Persons reportedly smoking fewer than 100 cigarettes in their lifetime are classified as nonsmokers. No mention is made of pipe or cigar smoking. Several different sources of ETS exposure are considered: husbands who smoke quantified in terms of years exposed and average number of cigarettes smoked per day; household members other than husbands who smoke, quantified by the sum of years exposed to each smoker; and coworkers who smoke, measured by the number of smokers sharing the "same closed space" as the subject. Presumably, childhood exposure is included in the household exposure assessment. For spousal smoking, single women are considered unexposed, whereas exposure of widowed or divorced women is based on the period when they were married. No attempts to verify exposure are mentioned.

For analysis of husband's smoking based on cigarettes per day, 64 out of 90 (exposed/total) cases and 70 out of 116 controls gives a crude odds ratio of 1.6 for 90 cases and 116 controls; 64 cases and 70 controls were exposed. The authors present results stratified by four exposure categories, which indicate no significant association ($p = 0.16$). Crude data for husband's smoking stratified by five levels of smoking duration (never, < 20, 20-29, 30-39, and 40+ years) yield a marginally significant increase in association with increasing duration ($p = 0.07$), with odds ratios of 1.0, 1.3, 1.3, 2.0, and 1.9, respectively. No statistically significant association was noted for ETS exposure from other household members ($p = 0.60$) or for exposure at work ($p = 0.13$), but the crude odds ratios for these exposures were 1.41 and 1.39, respectively. Stratification by level of intake for each of 16 food and nutrient groups yielded a significant negative (favorable) association with cereals ($p = 0.04$) and a possible association with fruits ($p = 0.11$).

Multiple logistic regression was then used to adjust results for age, education, and interviewer. An adjusted relative risk estimate of 1.92 (95% C.I. = 1.02, 3.59) was obtained for marriage to a smoker. After adjustment, trends for estimated lung cancer risk showed an increase with duration of exposure (average 16% per 10 years) and packs per day (6% per pack), but these were not statistically significant. No trend was observed for ETS in the household or workplace. Adjustment for other sources of air pollution had no effect on the analyses. Adjustment of dietary analyses for age, education, interviewer, and total energy intake indicated a significant decrease in estimated risk between highest and lowest quartiles of consumption of fruit ($RR = 0.33$; $p = 0.02$) and a nearly significant increase with consumption of retinol ($RR = 1.31$; $p = 0.06$), whereas beta carotene ($RR = 1.01$) and other dietary factors had no significant effect. Adding fruit consumption to the model for passive smoking increased the adjusted relative risk

for husband's smoking slightly, from 1.92 to 2.11. Stratification by lung cancer cell type yielded somewhat lower adjusted estimated relative risks for adenocarcinoma (2.04) than for squamous, small, and large cell cancer combined (2.58). No adjusted results were presented for other household or workplace exposure.

The authors' conclusion is best reflected in their abstract (shown in full above). Marriage of a nonsmoking woman to a smoker was associated with a relative risk for lung cancer of 2.1. Number of cigarettes smoked daily by the husband and years of exposure to husband's smoking were positively, but not significantly, related to lung cancer risk. There was no evidence of any association with exposure to smoking of other household members, and the association with exposure to passive smoking at work was small and not statistically significant. Dietary data indicated that high consumption of fruits was inversely related to the risk of lung cancer. Neither vegetables nor any other food group had an additional protective effect. The associations of lung cancer risk with passive smoking and reduced fruit intake were independent. Passive smoking was associated with an increase of the risk of all histologic types of cancer, although the elevation was more modest for adenocarcinoma.

It is noted that these findings are compatible with the relatively low incidence of lung cancer in the Greek population--a population with the highest per capita tobacco consumption in the world, but with a very high fruit consumption as well.

A.4.18.3. *Comments*

This study was generally well designed and executed. Set up specifically to address passive smoking and diet as etiological factors in lung cancer, it includes sufficient numbers of nonsmoking women to produce substantive results. Interviews were face-to-face, and no proxies were used, enhancing accuracy and comparability of responses, whereas the very low rate of refusal minimizes potential bias due to volunteer selection. Cases and controls were very similar demographically, were drawn from most of the same hospitals, and were matched temporally on time of interview, so comparability seems high. Furthermore, the study hospitals' patient population accounts for the majority of lung cancer and trauma patients seen in the Athens area, enhancing generalizability of results. Most lung cancers were histologically or cytologically confirmed, reducing chances for misclassification of disease status.

On the debit side, the apparently unblinded interviews could have been biased (although what can be accomplished toward that end is limited). Adjustment for interviewer in the analyses did not affect the results, however, and it is unlikely that all interviewers would share the same bias. Determination of what constitutes workplace exposure is vague, and childhood exposure is

not clearly differentiated from adult household exposure; these were notably the passive smoking categories, which showed the least association with lung cancer. ETS exposure in the workplace is analyzed with regard to trend (Table 2), with levels of exposure represented by "housewife" (zero exposure), "minimal," and "some," resulting in a p value of 0.13. Perhaps correctly, the authors cautiously note the evidence that ETS exposure is associated with increased risk (referring to Table 2 in general, not just exposure at work) but indicate that the differences are not large enough to be interpretable without controlling for other factors. An analysis of exposed versus unexposed for the workplace may have been useful, especially an adjusted analysis. Our calculation of the crude odds ratio for a comparison of "minimal" and "some" exposure at work is 1.7, which is suggestive.

Methodological rigor and thoroughness are particularly evident in the treatment of other factors that may affect risk. Despite the demographic similarity of cases and controls, the key demographic variables of age and education were nevertheless controlled for in the analyses, along with interviewer identity. The potential effects of air pollution, total energy intake, and other dietary factors on lung cancer incidence were examined, and the impact of cancer type was evaluated. An association of husband's smoking with lung cancer yielding an odds ratio of around 2 persisted with adjustment for those factors. The authors claim to have taken special effort to exclude ex-smokers from misclassification as never-smokers, taking account of this potential source of upward bias. No discussion was found, however, of what measures were taken to control misclassification of former smokers as never-smokers, beyond interviewing subjects about current and former smoking habits.

In summary, this study presents evidence of a level- and duration-dependent association between husband's smoking and lung cancer in a well-defined and highly comparable group of Greek cases and controls. Positive but nonsignificant relationships with general home or workplace passive smoking were observed, and there are indications that additional analysis of workplace exposure may be worthwhile. No effect of air pollution was observed. With regard to dietary factors, the large number of potential factors considered raises the issue of multiple comparisons. Fruit consumption may be a significant factor, but further evidence is needed to firmly establish this, particularly in view of the number of dietary factors explored. Dietary factors, however, do not account for the results for ETS exposure in this study. The results regarding spousal smoking cannot be readily attributed to bias, and they provide good quantitative data on the issue of passive smoking and lung cancer. This well-conducted study makes a valuable contribution to the evidence on lung cancer and ETS exposure.

A.4.19. KATA (No tier assignment is made on this study because the OR is undefined.)

A.4.19.1. *Author's Abstract*

"It is becoming noticeable in Japan that with increased incidence of lung cancer, there has been an increase in pulmonary carcinoma in women. Active smoking by women is increasing, while concern over passive smoking has been intensifying, and the effect of passive smoking on carcinogenesis has become a social problem. Regarding this effect, immunological and public health reports have appeared in Japan, but there have been few clinical reports, and detailed analysis of patients has been inadequate. Lung cancer presents a variegated histological picture, and presumably there are different carcinogenic factors for different histological types, although there have also been few reports on this subject. The effect of passive smoking probably varies depending on the regional environment and custom, and these factors should also be analyzed and included in the investigation. The present report describes our findings regarding the effects of smoking and familial aggregation of cancer in cases of pulmonary carcinoma in women."

A.4.19.2. *Study Description*

This study was undertaken in the Nara Prefecture, Japan, to investigate the effects of smoking and familial aggregation of cancer in cases of pulmonary carcinoma in women. Active smokers are included in the study, from which the nonsmokers are drawn for analysis. Matching is retained, however, in the nonsmokers.

For the whole study, subjects were drawn from a hospital (presumably the Nara Prefecture Medical University Hospital) during an unspecified period of time. Cases are female patients with histologically diagnosed lung cancer; controls are female patients with "nonmalignant" disease, matched 2 to 1 with cases on age plus or minus 2 years. It is not clear if only incident cases were used and if controls were density sampled. Case diagnoses were obtained from histological exam results, whereas control diagnoses were presumably from medical charts. Other information was collected from apparently unblinded "questioning," with an unspecified degree of reliance on proxy responses from family members.

A total of 25 cases and 50 controls are included in the study; no information on refusals is provided. Exclusion of active smokers leaves only 17 cases and, with retention of 1:1 matching, 17 controls. Mean ages for the total study population are 67.5 $\pm$ 8.8 years (67.6 $\pm$ 8.5 years) for cases (controls). The age distribution of ETS subjects is not discussed. Nonsmokers are defined by exclusion of "active smokers," with no delineation between former and current smokers. ETS exposure is defined as exposure to smoking more or less daily through living with a smoker. Three periods of ETS exposure are considered: current, past, and childhood, the last for those

"exposed since early childhood." Clearly these types are not mutually exclusive, although current sources of exposure are omitted from the "past" exposure category, even if present for a long time.

ETS exposure is quantified as cigarettes per day smoked times number of years. No mention is made of cigar or pipe smoking, nor of checks on exposure data. No distinction is made regarding marital status. Tumors occurring among current passive smokers were mostly adenocarcinomas (13/17), the remainder (4/17) being squamous or small cell cancers. Airway proximity was not specified. Excluding active smokers, all 17 cases were current passive smokers, compared with 14 out of 17 controls, for an odds ratio of 1.2, whereas past passive smoking characterized 16 of 17 cases and 17 of 17 controls, for an odds ratio of 0.9 (these odds ratios reflect the substitution of 0.5 for 0 in the exposure categories in which no subjects fall). Childhood passive smoking was reported in 13 of 15 cases and 7 of 15 controls (apparently all those for whom information was available), for an odds ratio of 7.4 ($p < 0.1$). None of the passive smoking odds ratios was statistically significant at the 5% level. No definite conclusion can be drawn from the present study, but there is a suggestion that passive smoking is associated with development of lung cancer in the Nara region. The effect of passive smoking that continued to the present time was especially marked, particularly in squamous cell carcinoma and small cell carcinoma. With adenocarcinoma, an effect of passive smoking in the past is suspected. Along with passive smoking, the association of some intrinsic factor (genetic tendency) to varying degrees in the different histologic types of lung cancer in women, especially in adenocarcinoma, is apparent.

A.4.19.3. *Comments*

The histological diagnosis of all cases, in combination with the apparent involvement of the researchers in the diagnoses, virtually eliminates the potential pitfall of misclassification of lung cancer cases. It also allows specific breakdowns by cell type. With regard to passive smoking, however, limitations related to exclusion of active smokers greatly reduced the study's potential.

In their initial analyses, the authors investigate passive smoking without excluding or stratifying on active smoking and report statistically significant associations with lung cancer and combined effects with family history of cancer. This is not a meaningful analysis, because the effects of active and passive smoking cannot be separated and passive smoke exposure probably correlates strongly with extent of active smoking. Excluding active smokers greatly reduces the available numbers of matched subjects and, in combination with the very high exposure prevalence among qualifying controls, makes the differences between cases and controls highly

unstable for all comparisons except for that of childhood exposure. Even here, with an estimated relative risk of 7.4, the results do not reach the 5% level of statistical significance, notwithstanding the problem of multiple comparisons. The authors also conduct cell-type-specific analyses, but these too fail to yield significant results. The extraordinarily high proportion of exposed present and past passive smoking controls is apparently a fluke, because the proportion is not as high in the total control subject population (or childhood passive smoking controls). Nevertheless, exposure was very common among controls. This indicates that the exposure criteria may be too lax or, alternatively, that the control population included a substantial proportion of persons with smoking-related diseases (controls being only stipulated not to have malignant disease).

In light of the minimal utility of the study's passive smoking analyses, detailed consideration of design strengths and weaknesses is unwarranted. Major points not already mentioned relate to information ascertainment and confounding. Interviews were apparently unblinded and, especially if conducted by the authors themselves, may thus have been biased toward uncovering exposure among cases (although the high prevalence of exposure among controls as well as cases argues against this). Furthermore, the extent of proxy interviews, potentially decreasing accuracy of exposure assessment, is unclear.

All subjects are female and, although results are not age adjusted, matching on age was retained for all analyses. No other risk factors except family history of cancer were considered, probably due to limited subject numbers, because much information on other factors was collected. Moreover, family history was considered only in the nonmeaningful analyses, which did not differentiate active and passive smokers. Thus, although the problems with numbers and exposure misclassification probably reduced the study's ability to detect whether an association exists, information bias and confounding could have biased results either up or down.

In summary, this study's data are consistent with an association of passive smoking, particularly childhood exposure, with lung cancer, but the results are too unstable and subject to potential bias to carry much weight, and the quantitative results must be viewed with extreme caution.

A.4.20. KOO (Tier 1)

A.4.20.1. *Author's Abstract*

"Lifetime exposures to environmental tobacco smoke from the home or workplace for 88 "never-smoked" female lung cancer patients and 137 "never-smoked" district controls were estimated in Hong Kong to assess the possible causal relationship of passive smoking to lung cancer risk. When relative risks based on the husband's smoking habits, or lifetime estimates of

total years, total hours, mean hours/day, or total cigarettes/day, or earlier age of initial exposure, were combined with years of exposure, there were no apparent increases in relative risk. However, when the data were segregated by histological type and location of the primary tumor, it was seen that peripheral tumors in the middle or lower lobes (or less strongly, squamous or small cell tumors in the middle of lower lobes) had increasing relative risks that might indicate some association with passive smoking exposure."

A.4.20.2. *Study Description*

This study, the second of four from Hong Kong, is based on a secondary data set of reported female never-smokers. The parent study from which the data on ETS subjects were drawn includes ever-smokers in a matched case-control study of 200 cases and 200 controls (Koo et al., 1984; also see Koo et al., 1983). Its objective is to assess the role of passive smoking as a potential etiological factor in the high incidence rate of lung cancer among Chinese females in Hong Kong. The current article emphasizes the quantitation of lifetime ETS exposure and the histological profile of lung cancer in exposed never-smokers.

In the parent study, cases are from the wards or outpatient departments of eight hospitals in Hong Kong during 1981-83. Controls are healthy subjects from the community, matched on age (within 5 years), district of residence, and type of housing (public or private). The cases are incident, and control sampling is density. Attrition due to selection or followup totals 26 (8 too ill to interview and 18 with secondary lung cancers), leaving 200 cases for interview. Face-to-face interviews of 1.5 to 2 hours were conducted directly with cases and controls. There was no restriction of cases by cell type of lung cancer. The ETS subjects extracted from the parent study include 88 cases and 137 controls. Of the 88 cases, 83 were confirmed by histology and 5 were "confirmed malignant." The number of squamous cell and small cell cases combined is 32 (23 ETS exposed; 72%); the corresponding figure for adenocarcinoma and large cell combined is 44 (31 ETS exposed; 70%); 12 cases are of another cell type or otherwise unspecified. For the 86 cases with available information, tumors were centrally located in 37 (25 ETS exposed; 67%) and peripherally in 46 (34 ETS exposed; 74%).

The term "never-smoker" applies to persons who have smoked a total of fewer than 20 cigarettes. Interview questions regarding exposure to ETS include cigarette and cigar smoking in the home during childhood, by the spouse and other cohabitants in adulthood, and workplace exposure. "ETS exposed" is technically used in several ways. For the comparison of exposed with unexposed ever-marrieds, it means the husband ever smoked in the wife's presence. For measures of exposure in terms of duration or rate (e.g., total years, hours/day, total hours, and cig./day),

there is some variation. For example, total years of exposure is derived by adding the years during which tobacco exposure occurred in the home or workplace. The total hours of exposure are calculated by multiplying the average hours per day of exposure by the years of exposure from each household smoker, or the amount of exposure at each workplace. The mean hours per day of exposure are found by adding the hours per day of home and workplace exposures and dividing this figure by the age of the subject. This figure is intended to approximate the average number of hours of exposure per day experienced by the subject, over her lifetime. Cumulative exposure is estimated by the total cigarettes smoked by family members, weighted by years of exposure.

When data are analyzed on the simple basis of whether a husband ever smoked in the presence of the wife, the crude and adjusted odds ratios are 1.55 (95% C.I. = 0.94, 3.08) and 1.64 (95% C.I. = 0.87, 3.09), respectively. The crude analysis applies to ever-marrieds only, which excludes three subjects. An adjusted analysis uses cigarettes per day smoked by the husband as the measure of ETS exposure. Conditional logistic regression was applied with stratification on district of residence, and housing type (public/private); model parameters were included for age, family history of lung cancer (yes/no), number of live births, and number of years since exposure at home or in the workplace.

The crude and adjusted methods give very similar odds ratios and confidence intervals, but the tests for trend differ substantially. The test for trend on the crude data is based on the Mantel-Haenszel test, using midpoints of the intervals for cigarettes per day smoked by the husband; the significance value is $p = 0.10$. The p value for trend in the adjusted analysis is 0.32. For analysis of data by other measures of exposure, as described above, the estimated odds ratio ranges between 1.0 and 4.1 across the three levels of the various measures of ETS exposure for both the analyses of the crude data and the adjusted analyses by conditional logistic regression, with two exceptions from analysis of the crude data for hours per day of exposure. The results are not statistically significant in most cases, because the sample sizes at each exposure level are small. The dose-response patterns observed are clearly sensitive to the measure of ETS exposure used, with several exhibiting an apparent peak at a low exposure level. Although the authors acknowledge that it was troubling to find the lack of a response pattern, no further explanation is given.

The authors did not detect a significant trend in the crude or adjusted odds ratio for the four lifetime measures of passive smoking (total years, hours, mean hours/day, cig./day). Although the odds ratio for the intermediate level exposures of hours per day and cigarettes per day was significant, the odds ratio at the highest levels of exposure for these two variables fell to a nonsignificant 1.0 to 1.2. In fact, the odds ratio for the highest exposure levels for three out of the four measurements were below all of those with lower exposures and ranged from a very weak

1.0 to 1.4. On the other hand, most of the crude and adjusted odds ratios were greater than 1.0. Measurements based on increasing intensity of exposure, defined as increasing years (or hours, or cig./day) by mean hours per day of exposure, also did not indicate a dose-response relationship. The analysis of total years of exposure with age of exposure did not suggest that earlier age of initial exposure and increasing years of exposure led to higher odds ratios.

It is concluded that when the lung tumors were segregated by histological type and location, the resulting analyses showed that peripheral tumors in the middle or lower lobes, and squamous or small cell tumors in the same lobes, exhibited better odds ratio patterns for passive smoking in terms of consistency, strength, and dose response. The odds ratio for total years, hours, and hours per day measurements of squamous and small cell lung tumors indicated consistently elevated risks with increasing exposure. This pattern was not found for any of the adjusted odds ratios for adenocarcinoma or large cell lung cancers.

The cases are divided into two groups histologically, those with squamous cell or small cell tumors and those with adenocarcinoma or large cell malignancies. Although none of the crude or adjusted analyses are found to be significant, it is concluded that an observed dose-response pattern seems to be more apparent in the squamous or small cell group. With regard to tumor location, some evidence suggests that peripheral tumors in the middle or lower lobes may be more common in passive smokers.

A.4.20.3. *Comments*

As described above, the data employed in the current study were taken from a larger retrospective study of female lung cancer in Hong Kong (Koo et al., 1984) that matched 200 cases and controls on age, district of residence, and housing type (private or public, an indication of socioeconomic status). Attention to detail and accuracy is evident in most aspects of the parent study. In particular, considerable effort was put into attempting to ascertain a better quantitative measure of exposure than used in preceding studies of ETS. Records were apparently verified to the extent possible to cross-check the accuracy of information collected, cancers were verified histologically, and analyses investigated questions related to the histological types and sites of tumors that may be related to passive smoking.

The never-smokers from the parent study, 88 cases and 137 controls, compose the secondary data set on which the current article is based. The matching of the subjects, of course, is no longer assured, leaving the comparability of the two groups uncertain. In addition, 60 (27%) of the subjects are widows, with no information provided on the distribution between cases and controls. Because spousal smoking is typically the variable on which ETS exposure pivots, this

may have some bearing on the response. However, an adjustment is made in some analyses for years since exposure to cigarette smoke ceased.

Some factors in the study itself may be contributing to the variable dose-response patterns. First, the number of ETS subjects is fairly small. When the subjects are classified into finer categories of exposure, the statistical variability is greatly increased (total of cases and controls is typically below 60). Second, questionable measurements of ETS may be causing some distortion. For instance, in the calculation of total years and total hours of ETS exposure, the years and hours were not added for simultaneous exposure to more than one smoker. Pipe smoking and the cigarette consumption levels of coworkers were excluded from the weighted average of the total cigarettes per day smoked by each household member. Thus, measurement appears to be based on the assumption that never-smoking women were exposed to ETS evenly throughout their lives (the authors claim that only subjects were used for which the exposure remained relatively regular during the lifetime, although no mention was found of cases being omitted because of failure to satisfy this criterion). Even if this assumption were valid, childhood and adulthood exposures are mixed as if the effects of exposure are interchangeable. Interestingly, differences between exposure in childhood and adulthood is one of the questions addressed in the article.

Although the objective is worthy, the attempt to quantitate exposure more precisely than previous studies appears to obscure more than to clarify. Some assumptions are not made very explicit, and their potential implications are not addressed well, which leaves some uneasiness about the conclusions. The authors have published at least three articles before this study that have some bearing on passive smoking and lung cancer, but their results are not discussed in the current study, even when the data analyzed are from the same source (Koo et al., 1983, 1984, 1985). Those articles, one of which describes the parent study (the 1984 citation), appear to reach somewhat different conclusions from this study regarding the predominance of histological type associated with passive smoking. Putting the current study's conclusions within the context of related prior work would enhance their clarity and interpretation.

Considering the reservations described above, the suggestion that the evidence indicates some association of passive smoking with the *location* of tumors is an overinterpretation of the data. A weaker conclusion is warranted, namely, that ETS exposure is associated with increased lung cancer incidence. What may be of most value in this study is the analysis based on the dichotomous classification of cases and controls as exposed or unexposed based on spousal smoking. Two concerns, however, will be reiterated. The ETS data are taken from a larger study not matched on smoking status, so they are unmatched. The study includes 80 widows, without mention of their distribution between cases and controls. In the adjusted analysis, an attempt is

made to take into account the number of years since last exposure, which would require some assumption regarding the change of risk relative to cessation of exposure. Both of these concerns are mitigated, however, by the similarity of the odds ratios and confidence intervals for the unadjusted and adjusted analyses. The care and thoroughness of the study in general make the results on the odds ratio for exposure to spousal smoke a useful contribution for evaluation with other study outcomes.

A.4.21. LAMT (Tier 2)

A.4.21.1. *Author's Abstract*

"In a case-control study in Hong Kong, 445 cases of Chinese female lung cancer patients all confirmed pathologically were compared with 445 Chinese female healthy neighborhood controls matched for age. The predominant histological type was adenocarcinoma (47.2%). The relative risk in ever-smokers was 3.81 ($p < 0.001$, 95% C.I. = 2.86, 5.08). The RRs were statistically significantly raised for all major cell types with significant trends between RR and amount of tobacco smoked daily. Among never-smoking women, RR for passive smoking due to a smoking husband was 1.65 ($p < 0.01$, 95% C.I. = 1.16, 2.35), with a significant trend between RR and amount smoked daily by the husband. When broken down by cell types, the numbers were substantial only for adenocarcinoma (RR = 2.12, $p < 0.01$, 95% C.I. = 1.32, 3.39) with a significant trend between RR and amount smoked daily by the husband. The results suggest that passive smoking is a risk factor for lung cancer, particularly adenocarcinoma in Hong Kong Chinese women who never smoked."

A.4.21.2. *Study Description*

This hospital-based case-control study was conducted in Hong Kong during 1983-86, to investigate whether smoking is a major risk factor for lung cancer in Hong Kong Chinese women and, if so, to determine the relationship between smoking and the histological types of lung cancer. Both active and passive smoking are of interest. The ETS subjects constitute only a subset of the whole study because it includes active smokers.

Eligible cases for the whole study are the 445 female patients with pathology-verified lung cancer admitted into eight large hospitals in Hong Kong during 1983-86. Cases were interviewed in person. Only a few eligible patients declined or were too ill to cooperate. An equal number of healthy neighborhood controls were identified and interviewed by density sampling. Controls were matched to cases on sex, age (± 5 years), and place of residence. The cases and controls include both never-smokers and ever-smokers, but smoking status was not used in matching.

"Never-smoker" means a person who never smoked as much as one cigarette per day, or its equivalent, for as long as 1 year.

A woman is "ETS exposed" if her husband smoked for at least 1 year while they lived together. If the husband was an ever-smoker, information on the type of tobacco and amount usually smoked per day by the husband and the duration of exposure was obtained. No information was collected on ETS exposure from other household members' smoking or smokers at work. Single (never-married) women were classified as nonexposed (6.8% and 5.2% in cases and controls, respectively). The treatment of widowed and divorced subjects is not explicitly addressed. Age and place of residence, as well as a series of other demographic variables, are similar between cases and controls.

The distribution of lung cancer by cell type in ETS cases is as follows: squamous cell, 12 of 27 (number exposed/total); small cell, 6 of 8; adenocarcinoma, 78 of 131; large cell, 7 of 9; and others or unspecified, 12 of 24. The corresponding crude odds ratios and 95% confidence intervals are 0.85 (0.35, 2.06), 3.00 (0.53, 16.90), 2.12 (1.32, 3.39), 3.11 (0.50, 19.54), and 1.08 (0.41, 2.82), respectively. The odds ratio for all cell types combined is 1.65 (1.16, 2.35), based on 115 of 199 (exposed/total) cases and 152 of 335 controls. The data for all cell types together, and for adenocarcinoma alone, are both significant at $p < 0.01$. No information is available on the airway proximity of tumors.

Trend tests were conducted for the amount smoked daily by the husband, categorized in terms of cigarettes as "nil," 1 to 10, 11 to 20, and 21 or more. The odds ratios in the three exposure categories are 2.18, 1.85, and 2.07, respectively, when all cell types are included. For adenocarcinoma alone, the corresponding odds ratios are slightly higher (2.46, 2.29, and 2.89, respectively). The dose-response relationship does not appear to increase between the lowest dose and the highest dose, but a test for trend is significant ($p < 0.01$ for all cell types and $p < 0.001$ for adenocarcinoma alone) when the "nil" group is included. No adjusted analyses are given.

The authors conclude that the significant trends observed between relative risk and amount smoked daily by husband, for all cell types combined and for adenocarcinoma alone, support the view that the observed association between ETS exposure and lung cancer is likely to be causal.

A.4.21.3. *Comments*

This study is the fourth of the Hong Kong epidemiologic inquiries into tobacco smoke as a possible etiological factor in the high rate of lung cancer, particularly adenocarcinoma, among women. Active smoking was included as well as passive smoking because the previous studies in

Hong Kong were inconclusive. According to the authors, this led to the hypothesis that smoking is not a risk factor for adenocarcinoma in Hong Kong Chinese women. Matching of controls to cases was conducted for the whole study, including active smokers. It cannot be assumed, however, that the never-smokers alone, who constitute 45% of the cases and 76% of the controls, are matched.

Overall, the study demonstrates care in planning and execution. The sample size of ETS subjects is moderately large, providing higher statistical power than the previous Hong Kong studies. All cases were pathologically confirmed as primary lung cancers, essentially eliminating the potential for error due to disease misclassification. Odds ratios were calculated by histological type for comparison. Cases and controls were interviewed personally, apparently with no proxy respondents and very few refusals, which reduces the potential for response bias. The exclusive use of incident cases helps to control potential selection bias, and density sampling of controls contributes to comparability of cases and controls. For the whole study, including smokers, healthy controls were matched to cases by sex, age, and neighborhood of residence. The mean and standard deviation of ages are nearly identical in cases and controls. According to the authors, a comparison by other demographic variables showed that, for the whole study, cases and controls were also comparable in place of birth, duration of stay in Hong Kong, level of education, marital status, and husband's occupation. Further attention to detail is evident in the clear definitions of "never-smoker" and "ETS exposure," essential to accurate classification of subjects for analysis and interpretation. Single women were treated as not exposed to husband's smoking, which could be a source of bias because these women may be exposed from other household members. This possibility was considered, however, because the article reports that similar results were obtained when single women were excluded.

In summary, the crude odds ratios vary between 2.1 and 3.1 for small cell carcinoma, adenocarcinoma, and large cell carcinoma, with adenocarcinoma significant at $p < 0.01$. The odds ratios are consistently elevated at all three intensity levels of spousal smoking, varying between 1.8 and 2.9, with the odds ratio for adenocarcinoma alone somewhat higher than for all cell types combined. There is no apparent upward trend, however, from the lowest smoking intensity (1-10 cig./day) to the highest (21+ cig./day). These statistical results are ostensibly suggestive of an association between ETS exposure and lung cancer incidence, but they are based on only crude data with cases and controls unmatched, even on ages. Nor are statistical methods used that could adjust for matching variables, or other factors, in the data analysis (e.g., by stratification or logistic regression). Although this study was carefully conducted in most respects, the disregard for potential confounding effects leaves the authors' conclusion uncertain.

A.4.22. LAMW (Tier 3)

(*Note*: This study is part of the thesis of LAM Wah Kit submitted to the University of Hong Kong for the M.D. degree in 1985, entitled *A Clinical and Epidemiological Study of Carcinoma in Hong Kong*. The description given below is from Chapter 7 of the thesis only, entitled *Case-Control Study of Passive Smoking, Kerosene Stove Usage and Home Incense Burning in Relation to Lung Cancer in Nonsmoking Females (1981-84)*, which the author submitted in response to our request. The abstract below was prepared by the reviewers, since none was available from the author.)

A.4.22.1. Abstract

The study's objective is to investigate the hypothesis that an inhaled carcinogen may be related to the high incidence of centrally situated adenocarcinoma of the lung observed in nonsmoking female patients. Air pollution is probably not an important factor because it presumably affects both men and women. Most women in Hong Kong either stay at home or join the work force in commerce, services, or manufacturing, which are not associated with any known risk factor for lung cancer. Three etiological activities, all predominantly in the home, are considered in this study: passive smoking, kerosene stove cooking, and home incense burning. No evidence was found to implicate exposure to kerosene stove fumes or incense burning in centrally located adenocarcinoma. There is suggestive evidence of an association between ETS exposure from smoking husbands and occurrence of peripheral (but not central) adenocarcinoma. Why the location tends to be peripheral instead of central is speculative.

A.4.22.2. *Study Description*

(*Note:* The details of the study are not complete in the material provided. Some useful information, however, is available.)

The cases are all of the Chinese female patients admitted to the University Department of Medicine, Queen Mary Hospital, Hong Kong, between January 1981 and April 1984 with histologically and/or cytologically confirmed carcinoma of the lung of the four major cell types. Care was taken to exclude patients with secondary carcinoma of the lung; otherwise, all patients were included. The controls are Chinese female patients admitted to the orthopedic wards of the hospital in the period 1982-84, comparable to lung cancer patients in age and social class. Patients with pathological fractures due to smoking-related malignancies or with peripheral vascular disease-related orthopedic conditions were excluded.

Both cases and controls were patients of the third-class general wards, mostly from the lower income group. All subjects were interviewed in person. The questions covered dialect group, occupation, smoking habits, passive smoking, domestic cooking with kerosene, and home incense burning, in the form of a standardized questionnaire. For very ill patients, or for patients who spoke a dialect other than Cantonese or Mandarin, the next of kin was interviewed, with the patient as interpreter. The whole study, including active smokers, contains 161 cases and 185 controls, similar in age (median age is 67.5 [66] for cases [controls]), socioeconomic status (as measured by occupation and years of schooling), and recent residence. The author considered it unnecessary to stratify on these or any other variables.

The ETS subjects consist of 75 (144) cases (controls), including 16 (14) never-married cases (controls). The distribution of cases by cancer cell type is as follows: squamous cell (7), small cell (3), large cell (5), and adenocarcinoma (60). Questions related to ETS exposure include details on each smoker in the home (husband, others, mother, and father), amount smoked per day, hours of ETS exposure per day, and number of years smoked. Information about exposure in the workplace includes size of the workplace, number of coworkers who smoke, exposure time/day, and number of years of exposure at work.

Only the data for adenocarcinoma, the predominant cell type observed and the pathogenesis of interest, are analyzed. The number of cases is 37 out of 60 (exposed/total), and the number of controls is 64 out of 144, where ETS exposure refers to spousal smoking. The odds ratio (calculated by the reviewers) is 2.01 (95% C.I. = 1.09, 3.72). The author divides the cases by location according to airway proximity, with 18 of 32 (exposed/total) located centrally and 19 of 28 in peripheral regions. The respective risk ratios are 1.61 and 2.64. Two tests were conducted for significance, including the Bayesian risk ratio analysis and a test of the slope for the exposure parameter in a simple logistic regression model. The significance levels are 0.11 and 0.19, respectively, for the central location and 0.01 and 0.02, respectively, for peripheral tumors. The test results differ widely for total passive smoking (home or workplace). For the central location, the respective significance levels are 0.09 and 0.3; for peripheral locations, the corresponding values are 0.03 and 0.15. It is suggested that the different outcomes for the two tests applied to total passive smoking may be due to a nonlinear logistic dose-response curve or to errors in assessing the level of exposure due to incomplete information. The apparent association between passive smoking and peripheral adenocarcinoma (and not central tumors) in the cases was unexpected. Based on the available raw data, exposure to a smoking spouse, cohabitant, and/or coworker is associated with an odds ratio of 2.51 (95% C.I. = 1.34, 4.67) for all cell types combined. The author concludes that there is a suggestion of passive smoking associated with peripheral adenocarcinoma, particularly passive smoking attributable to smoking husbands.

Kerosene and incense burning were not found to be associated with adenocarcinoma, either central or peripheral.

A.4.22.3. *Comments*

Cases and controls appear to be comparable in age, socioeconomic status, and recent residence for the whole study (including active smokers), although the study design is not matched on these or other variables. Some discrepancies between cases and controls are apparent, however, such as a higher percentage of cases than controls working outside the home (41% compared with 28%). The figures for nonsmokers alone (i.e., the ETS subjects) are not given, so comparability is uncertain for analysis of ETS exposure. Care has been taken to include only primary lung cancer patients among the cases, essentially eliminating this potential source of bias. Subjects were personally interviewed, with apparently only a small number of proxy respondents required, although no figure is given. The interviews apparently were not blinded, but that may not have been feasible considering the nature of the questions asked and the use of noncancer patients as controls. Considerable attention is given to histological type of cancer and the location in terms of airway proximity.

The author is particularly interested in the etiology of adenocarcinoma and focuses discussion on the adenocarcinoma cases to the exclusion of others. Although the raw data pertaining to other cell types are tabulated, more attention to those types in the analyses would have been useful. The adenocarcinoma cases are categorized further by central and peripheral location, which are analyzed separately. Again, a combined analysis would be useful (the reviewers calculated the crude odds ratio for the combined data, which is given above). Although logistic regression is employed as one of the two statistical tools for analysis, factors that may differ between cases and controls are not included. Potential confounding variables need to be controlled for, by logistic regression, poststratification, or otherwise. To claim that cases and controls are similar in potential confounding characteristics does not alleviate the need to adjust for them in the analysis, particularly when the ETS data are a subset of the larger data set to which reference is made. Similarly, in testing three factors for an association with lung cancer (passive smoking, cooking with kerosene, and burning incense), it would be useful to conduct an analysis that will allow evaluation of the effect of each after adjustment for the other two.

The suggestive evidence that passive smoking is more likely associated with adenocarcinoma in peripheral rather than central locations may be logical but is weak, especially considering the lack of analytical rigor. The proportion of ETS-exposed cases of adenocarcinoma is 18 of 32 (56%) for central locations and 19 of 28 (68%) for peripheral locations. This difference

is not statistically significant (p = 0.26 by Fisher's exact test). Consequently, the "apparent association" between passive smoking and peripheral adenocarcinoma (and not central tumors) may well be due to chance alone. There is suggestive evidence in the data that passive smoking may be associated with lung cancer (OR = 2.01, p < 0.03 for a one-sided test), but that is based only on the crude odds ratio in unmatched data and needs to be confirmed by a more thorough evaluation of the data that takes potential confounders into account. Overall, this study provides some suggestive evidence for an association between passive smoking and lung cancer. Potential confounders (including age) have not been controlled for, however, so attribution of the elevated odds ratio to ETS exposure is uncertain.

A.4.23. LEE (Tier 2)

A.4.23.1. *Author's Abstract*

"In the latter part of a large hospital case-control study of the relationship of type of cigarette smoked to risk of various smoking-associated diseases, patients answered questions on the smoking habits of their first spouse and on the extent of passive smoke exposure at home, at work, during travel and during leisure. In an extension of this study an attempt was made to obtain smoking habit data directly from the spouses of all lifelong nonsmoking lung cancer cases and of two lifelong nonsmoking matched controls for each case. The attempt was made regardless of whether the patients had answered passive smoking questions in the hospital or not.

Among lifelong nonsmokers, passive smoking was not associated with any significant increase in risk of lung cancer, chronic bronchitis, ischemic heart disease, or stroke in any analysis.

Limitations of past studies on passive smoking are discussed and the need for further research underlined. From all the available evidence, it appears that any effect of passive smoke on risk of any of the major diseases that have been associated with active smoking is at most small, and may not exist at all."

A.4.23.2. *Study Description*

This study was undertaken in England, essentially from 1979 to 1983. Its stated objective is to investigate the relationship between passive smoking and risk of lung cancer in nonsmokers. It is an outgrowth, however, of a hospital-based case-control study to assess whether the risk of cardiorespiratory disease associated with smoking varies by type of cigarette smoked. It was initiated in 1977 in 10 hospital regions in England. In 1979, interviewers began gathering information on passive smoking as well in four of the regions. Then in 1982, this case-control

study of the effects of passive smoking was begun using nonsmoking cases identified by the ongoing cardiorespiratory effects study. For the new study, spouses of cases and specially selected controls were interviewed regarding smoking habits. Previously collected data on passive smoke exposure obtained from patients back to 1979 were used.

Basically, two substudies were conducted. One used the data obtained directly from hospitalized cases and controls to address several sources of passive smoke, including spousal (henceforward the "passive smoking" study); the second substudy used data obtained from the spouses of cases and controls along with corresponding information from the patients themselves, when available, to address spousal smoke exposure only (henceforward the "spousal smoking" study). Cases for the passive smoking study were currently married lifelong nonsmokers diagnosed with lung cancer (of any cell type), chronic bronchitis, ischemic heart disease, or stroke in one of four participating hospital regions. Controls were currently married lifelong nonsmoker inpatients diagnosed with a condition definitely or probably not related to smoking and individually matched on sex, age, hospital region, and, when possible, hospital ward and time of interview. Thus, density sampling was used when possible. For the spousal smoking study, previously married patients were excluded; the same criteria otherwise applied, except that controls were now matched on sex, age decade, and--as far as possible--hospital and time of interview.

Diagnoses were obtained from medical records. Exposure data were obtained through apparently unblinded, presumably face-to-face interviews with inpatients and their spouses. A total of 3,832 married cases and controls were interviewed regarding passive smoking through 1982; it is unclear how many potential subjects refused or died before interview. Only 56 of these were married lung cancer cases meeting the spousal smoking study criteria. Spousal interview data were obtained for 34 of these cases and 80 controls; interviews were refused by the remainder. Although matching of cases and controls was initially carried out, it was not retained in the analysis, and no demographic comparison of cases and controls used in the analyses is provided. Diagnoses were apparently drawn from patients' charts; provisional diagnoses were used where no final diagnosis was specified, no data on diagnostic technique(s) or histology was presented, and no diagnostic verification was reported.

The patient population consists of never-smokers, defined as lifelong nonsmokers, which presumably excludes cigar and pipe smokers. Exposure to ETS is approached in several ways. The primary exposure is that of a spouse smoking manufactured cigarettes at some point over the course of a marriage. Spousal smoking in the 12 months before interview also was assessed. In addition, "regular" exposure to passive smoke in various situations (i.e., at home or work, during travel or leisure) was assessed. The first two exposures were quantified in numbers of cigarettes

smoked per day, the others in terms of "not at all, a little, average, or a lot." Thus, it appears that cigar and pipe smoking may not have been included in the spousal smoking exposures. Comparison of individual responses regarding spousal smoking status by patients and their spouses revealed a high degree of concordance (97%) for smoking during the past 12 months and a substantial concordance (85%) for smoking during marriage. No other checks on exposure data were reported.

The ETS patient data set includes 56 cases and 112 controls who met the initial study criteria. Not all of these answered each passive exposure question, however, and not all met the criteria for the spousal interview study. Similarly, spouses of 34 cases and 80 controls provided exposure information of varying completeness. Thus, the numbers involved in each analysis varied considerably. For smoking during marriage, data obtained directly from spouses indicated that for males and females combined, 24 of 34 lung cancer cases and 51 of 80 controls were exposed, which yields a crude odds ratio of 1.4 for spousal smoking. With standardization for age, an odds ratio of 1.33 (95% C.I. = 0.50, 3.48) was reported. Data obtained from qualifying patients, in contrast, revealed 13 of 29 cases and 27 of 59 controls to be exposed, yielding a crude *and* adjusted odds ratio of 1.00 (95% C.I. = 0.41, 2.44). Stratification by gender yielded adjusted odds ratios from spousal interview data of 1.60 (0.44, 5.78) and 1.01 (0.23, 4.41) for females and males, respectively, with corresponding odds ratios from patient interview data of 0.75 (0.24, 2.40) and 1.5 (0.37, 6.34). When spouses identified as smokers by interview with either source were classified as exposed, an odds ratio of 1.00 (0.37, 2.71) was obtained for female subjects. For the larger inpatient passive smoking study population, age-standardized odds ratios for passive smoke exposure at home, at work, during travel, and during leisure revealed no consistent associations, with as many negative as positive relationships observed after adjustment for both age and whether still currently married. The same inconsistency held true for spousal smoking during the last 12 months and during the whole marriage. Adjustment for working in a dusty job reportedly did not affect the conclusion that passive smoking was not associated with risk.

Spousal smoking was slightly negatively associated with chronic bronchitis, ischemic heart disease, and stroke, whereas a combined ETS exposure index was negatively associated with heart disease but positively associated with bronchitis and stroke.

The author concluded that the findings appear consistent with the general view, based on all the available evidence, that any effect of passive smoking on risk of lung cancer or other smoking-associated diseases is at most quite small, if it exists at all. The marked increases in risk noted in some studies are more likely to be a result of bias in the study design than of a true effect of passive smoking.

A.4.23.3. *Comments*

The heart of this study is the spousal interview investigation of lung cancer and spousal smoking. Only 34 case spouses and 80 control spouses, and even fewer of the corresponding cases and controls themselves, are included, which gives the study low statistical power. Because the study began with hospital inpatient married lifelong nonsmokers, and matching on several key factors was employed, good comparability of cases and controls would seem readily achievable. No case-control demographics are provided, however, and matching is abandoned in the analyses. The occurrence of interview refusals and omitted responses (themselves a potential source of selection and information bias) may have contributed to the decision to abandon matching, with the aim of preventing further substantial reduction in numbers through exclusion of unmatched subjects. As a result, the comparability of the cases and controls is uncertain. At least all are drawn from the same four hospital areas within a fairly limited timespan, which, in combination with the other study criteria, reduces the likelihood of serious noncomparability.

Numerous opportunities for misclassification of disease and exposure status are present. Current working diagnoses are apparently drawn from patient charts without verification, and controls are selected from patients with diagnoses judged either probably or definitely not associated with smoking by unspecified criteria. This creates considerable potential for misclassification, both through inaccuracies in diagnoses generally and through inclusion of smoking-related diseases in the control group particularly, which would produce a downward bias in results. Exposure misreporting and recall problems would seem least likely where spouses are interviewed directly about exposure within the past 12 months. Results for this situation are not presented, although they are reportedly similar to those for smoking during marriage.

The larger inpatient study elicited smoking data from patients, and only for their *first* spouse for patients who had remarried; thus, exposure occurring in subsequent marriages is not addressed. In addition, no information on duration or level of smoking in marriage is used in any of the spousal smoking analyses. The most likely result of these problems is nondifferential misclassification resulting in a bias toward the null. For general estimated home, work, travel, or leisure exposure to passive smoke, rough quantification *is* attempted by having patients categorize their exposure as "not at all, a little, average, or a lot." By necessity, this is a very subjective evaluation, and people more acclimated to smoke and tolerant of exposure might well tend to characterize a given amount of exposure as less severe than would a person less tolerant of smoke who more actively avoids exposure. This tendency would produce a bias toward negative association.

Standardization for age and restriction of cases and controls to currently married lifelong nonsmokers should control the effects of age, marital status, or active smoking, although misreporting of current or former active smoking cannot be ruled out entirely. Dusty occupation reportedly had no effect on the larger inpatient study results. Potential effects of race, socioeconomic status, diet, cooking habits, or any additional factors were not addressed.

One might expect the most accurate reporting of spousal smoke exposure when spouses are interviewed directly regarding their own smoking habits, and the most inadvertent misclassification when patients are queried about the smoking status of their first marital partner only. Analyses along these lines yielded slightly positive associations with smoking for the former and negative with the latter approach. No consistent pattern of association was seen for other sources and lung cancer, although high combined exposure scores were associated positively with chronic bronchitis and stroke and negatively with ischemic heart disease.

In summary, this study presents equivocal results that neither strongly confirm nor refute the hypothesis that passive smoking mildly increases risk of lung cancer. The quality of the study, however, is a limitation. The discrepant results for subject-supplied data (OR = 0.75) and spouse-supplied data (OR = 1.60), varying degrees of completeness of information on subjects, and the subjective nature of questions regarding ETS exposure limit confidence in the study's data and, consequently, the results of its analysis of those data.

A.4.24. LIU (Tier 4)

A.4.24.1. *Author's Abstract*

"In Xuanwei County, Yunnan Province, lung cancer mortality rates are among the highest in China in both males and females. Previous studies have shown a strong association of lung cancer mortality with indoor air pollution from 'smoky' coal combustion. In the present case-control study, 110 newly diagnosed lung cancer patients and 426 controls were matched with respect to age, sex, occupation (all subjects were farmers), and village of residence (which provided matching with respect to fuel use). This design allowed assessment of known and suspected lung cancer risk factors other than those mentioned above. Data from males and females were analyzed by conditional logistic regression. In females who do not smoke, the presence of lung cancer was statistically significantly associated with chronic bronchitis (OR = 7.37, 95% C.I. = 2.40, 22.66) and family history of lung cancer (OR 4.18, 95% C.I. = 1.61, 10.85). Females' results also suggested an association of lung cancer with duration of cooking food (OR 1.00, 9.18, and 14.70), but not with passive smoking (OR 0.77, 95% C.I. = 0.30, 1.96). In males, lung cancer was significantly associated with chronic bronchitis (OR 7.32, 95% C.I. = 2.86, 20.18),

family history of lung cancer (OR 3.78, 95% C.I. = 1.70, 8.42), and personal history of cooking food (OR 3.36, 95% C.I. = 1.27, 8.88). In males, a dose-response relationship of lung cancer with smoking index (years of smoking/amount of smoking) was shown by risks of 1.00, 2.61, 2.17, and 4.70."

A.4.24.2. *Study Description*

This study was undertaken in Xuanwei County of China's Yunnan Province, a county whose lung cancer mortality rates are among the country's highest and wherein burning of smoky coal indoors in unventilated pits is a common practice. The study sought to assess "the influence of factors other than type of fuel on the occurrence of lung cancer in Xuanwei."

Cases of newly diagnosed lung cancer occurring among farmers at hospitals and clinics in Xuanwei between November 1985 and December 1986 were identified as potential study subjects. Up to five controls were identified for each case, depending on availability after matching on age (± 2 years), gender, and village of residence. A total of 112 cases were identified, from which 2 were excluded due to unknown addresses. Of 452 candidate controls, 26 were excluded due to erroneous questionnaire responses. All subjects were interviewed face-to-face by trained personnel using a standardized questionnaire, and blinding extended to both interviewers and interviewees.

The final study groups consist of 54 (56) female (male) cases and 202 (224) female (male) controls. Mean age is 52 years for both cases and controls, who are also similar in family size, ethnicity, birthplace, dwelling type, and type of fuel used (smoky coal, wood). Separate breakdowns for males and females are not provided. Very few of the cases (19/110 = 17%) were histologically or cytologically diagnosed, and no verification of diagnosis or exclusion of secondary tumors was undertaken (except to monitor mortality among some of the cases).

Exposure to ETS was not evaluated for males. Among females, only one subject (a control) reported ever having smoked, so the ETS population of females effectively consists of never-smokers. Subjects were classified as exposed to ETS if their household contained at least one smoker. Exposure is not quantified, and it is unclear whether former or only current exposure is intended. No checks on exposure status or consideration of marital status are mentioned, and no histological data are presented.

The proportion of exposed female subjects is 45 out of 54 (176/202) for cases (controls), yielding a crude odds ratio of 0.74. A conditional logistic regression analysis adjusted for other risk factors (presumably the other factors referred to are age-began-cooking and years-of-

cooking) gives an odds ratio of 0.77 (95% C.I. = 0.30, 1.96). No further analyses of ETS exposure are provided.

Four non-ETS factors are significantly associated with lung cancer among females: family history of lung cancer (OR = 4.18; 95% C.I. = 1.61, 10.85), personal history of bronchitis (OR = 7.37; C.I. = 2.40, 22.66), age-began-cooking (OR = 2.44-1.03, but with a reversing and nonsignificant dose-response), and years-of-cooking (OR = 2.49-2.25, nonsignificant trend). Among males, significant positive associations were noted for total smoking index, often-cooking-own-food, family history of lung cancer, and history of chronic bronchitis, whereas age-began-smoking, years of smoking, and intensity of smoking showed modest but nonsignificant associations with lung cancer.

The authors conclude that "it is quite conceivable that the large amount of air pollutants inhaled during indoor smoky coal burning in Xuanwei partly overwhelm the carcinogenic effect of tobacco smoking" and "may also overwhelm the carcinogenic effect of passive smoking." "Our results disclose important associations of lung cancer with factors other than fuel type and therefore indicate that those factors must be considered in any comprehensive, quantitative risk assessment of lung cancer in Xuanwei. Our results also confirm indirectly that smoky coal pollution is an important determinant of lung cancer in Xuanwei."

A.4.24.3. *Comments*

This modestly sized study was not designed to test for effects of ETS exposure. Rather, it is a hypothesis-generating exercise aimed at covering a broad range of possible risk factors. Within that context, the study has considerable merit, but as an investigation of ETS it has numerous flaws.

Restriction to farmers minimizes concerns with occupation and overall lifestyle, and control selection, including matching on age, gender, and village, produced demographically comparable case and control populations for males and females combined despite the enigmatic exclusion criterion for controls. It is unknown, however, whether the groups remain comparable after subdivision into males and females.

The use of newly diagnosed cases reduces potential selection bias due to inclusion of prevalent cases, but the heavy reliance (83%) on clinical and radiological diagnosis and the absence of independent confirmation or exclusion of secondary tumors introduces a strong potential for misclassification of disease and precludes analyses by cell type. The observation that followup of a number of lung cancer patients revealed that almost all died within 6 months of diagnosis does little to confirm diagnostic validity, contrary to the authors' interpretation. Such presumably

random misclassification would make detection of an existing ETS-lung cancer association more difficult.

Exposure data collection procedures, particularly the exclusive use of face-to-face interviews without resort to proxies and the blinding of both interviewers and subjects, are laudable. For ETS, however, the exposure measure used is nonspecific and nonquantitative. Complications due to past exposure and differences in degree or duration could distort the observed disease-exposure relationship, probably biasing results toward no effect.

Potential confounding is not adequately addressed in the statistical analysis. The authors are particularly concerned with indoor smoky coal burning due to the known strong correlation between smoky coal use and lung cancer mortality in Xuanwei. Wishing to focus their investigations on factors other than smoky coal, they matched cases and controls on village, which "provided effective matching on fuel type." But because age and a host of other demographic factors, as well as smoky coal consumption, were comparably distributed in cases and controls (see study description), these factors were not considered further in the data analysis. This is a serious flaw, for pair matching was not retained in the analysis; thus, none of the above factors is effectively controlled for. The conditional regression analyses do control for risk factors other than those cited above, but exclusion of age, fuel type (e.g., smoky coal), and degree of exposure to fuel fumes may produce misleading results.

The presence of other significant risk factors for lung cancer makes detection of an effect from ETS, if present, less likely. Masking by the presence of smoky coal and other factors in the study environment is probably a factor in the remarkably weak association between active smoking and lung cancer among study males (adjusted OR = 1.36). If even an effect of active smoking remains largely obscured under study conditions, it is unlikely that an effect of ETS would be detected. Supporting these concerns are other recent studies in Xuanwei County that have confirmed widespread smoky coal use (e.g., 100% of households in Cheng Guan commune before 1958) and serious indoor air pollution with combustion byproducts, including mean indoor benzo[a]pyrene (BaP) levels of 9-15 ng/m^3 in two communes using smoky coal during fall of 1983 (Mumford et al., 1987). Prior use of smoky coal at age 12 is associated with an OR of 3.7 for lung cancer in pair-matched female residents (Chapman et al., 1988). He et al. (1991), who report a strong association between indoor BaP and lung cancer, conclude that indoor air pollution appears to be the strongest risk factor for lung cancer in Xuanwei females.

Overall, this study makes important contributions to its principal objectives but is not helpful in assessing ETS and lung cancer. It is observed, for example, that persons in areas of Xuanwei with high lung cancer rates (and high smoky coal consumption) may inhale more BaP by spending 8 hours indoors than by smoking 20 cigarettes. Due to such factors, the authors observe,

"the effect of passive smoking on lung cancer may depend on local environmental factors and results obtained in a given region therefore may not be applicable to other regions." Avoidance of areas atypically rich in competing exposures and careful control of potential confounders and interactive risk factors must be key objectives in studies of ETS and lung cancer.

A.4.25. PERS (Tier 1)

A.4.25.1. *Author's Abstract*

"The relation between passive smoking and lung cancer was examined by means of a case-control study in a cohort of 27,409 nonsmoking Swedish women identified from questionnaires mailed in 1961 and 1963. A total of 77 cases of primary carcinoma of the bronchus or lung were found in a followup of the cohort through 1980. A new questionnaire in 1984 provided information on smoking by study subjects and their spouses as well as on potential confounding factors. The study revealed a relative risk of 3.3, constituting a statistically significant increase ($p < 0.05$) for squamous cell and small cell carcinomas in women married to smokers and a positive dose-response relation. No consistent effect could be seen for other histologic types, indicating that passive smoking is related primarily to those forms of lung cancer that show the highest relative risks in smokers."

A.4.25.2. *Study Description*

This case-control study, undertaken to explore the role of passive smoking in lung cancer, is based on cohorts of Swedish women assembled prior to 1963. Nonsmokers were drawn from these cohorts to create matched case and control groups.

Cases are nonsmoking Swedish women included in the Swedish National Census or Twin Registry who responded to smoking status questionnaires in 1961-63 and who subsequently developed primary lung or bronchial cancer by 1980. Two control groups were cumulatively sampled from National Census or Twin Registry subjects who did not develop lung or bronchial cancer. In group 1, two controls were matched to each case on year of birth ($\pm$ 1 year). In group 2, two controls were matched to each case (2:1) on year of birth ($\pm$ 1 year) and vital status in 1980. Thus, there were 58 cases and 232 controls from the National Census and 34 cases and 136 controls from the Twin Registry. A followup questionnaire that included questions on spousal and parental smoking habits was distributed to each subject or the next of kin in 1984. Out of 92 cases of tracheal, bronchial, lung, or pleural cancer occurring by 1980, 15 cases in which a diagnosis of primary cancer of the lung or bronchus was not established were excluded. Exclusion of women indicated to be active smokers according to the 1984 questionnaire, or for whom ETS

Logistic regression analyses reportedly produced the same results as did the stratified analyses. In addition, occupation, household radon, and urban or rural status had no significant effect. It is notable, however, that for all cancers combined, the odds ratio for radon exposure is 1.4 (0.4, 5.4), the odds ratio for spousal smoking is 1.2 (0.6, 2.6), and the odds ratio for radon and spousal smoking combined is 2.5 (0.8, 8.5). No separate analyses for squamous and small cell cancer are provided for radon and other potential confounders. The authors conclude that exposure to ETS is related primarily to the forms of lung cancer that show the highest relative risks in smokers. The results are internally consistent.

A.4.25.3. ***Comments***

Although based on cohorts assembled for other purposes, this case-control study was specifically designed to investigate passive smoke exposure. Thus, all participants are ETS subjects that are matched. Matching criteria are rather modest--birthdate (± 1 year) for control group 1 and birthdate and vital status for control group 2. Because the study targeted all cases detected in the same cohorts from which matching controls were randomly drawn, good comparability of cases and controls is likely. No demographic comparisons of cases and controls for whom ETS information was available--and thus who constituted the analytical subjects--were provided to confirm this, however. Data on active smoking among subjects were collected both at the start and after the end of mortality monitoring, providing an opportunity to verify the nonsmoking status over time and exclude individuals whose status had changed (apparently those reported in 1984 to have smoked daily for at least 2 years were so excluded). Thus, the probability of significant misclassification of active smoking status is low. Data on passive smoking were collected only after the end of mortality monitoring and by necessity employed proxy respondents extensively, so some misclassification of exposure is likely. Self-administration of questionnaires eliminates interviewer bias as a source of error, making misclassification less likely to be systematic, but preferential recall of smoke exposure by relatives of cancer victims could have produced a bias. Misclassification of disease is unlikely to have been a problem because most cases were histologically diagnosed and secondary lung cancers were excluded.

Consideration of spousal smoke exposure only in their longest marriage among women married more than once means that some of the unexposed group probably had substantial exposure to spousal smoking, creating a bias toward no association. Classification of all never-married women as unexposed despite possible smoking by cohabitants creates the same bias. Few subjects (less than 20%) were single, but the frequency of remarriage is unknown; therefore,

exposure information was not available, eliminated a further 10 cases. Active smoking and lack of exposure information eliminated 21 of the 368 controls initially assembled. Histological confirmation was available for 64 of the 77 cases with primary lung or bronchial cancer; 12 cases were cytologically confirmed, and the remaining case was verified at autopsy.

Never-smokers are subjects who report that they have never smoked any form of tobacco. A woman is ETS exposed if she has ever been married to a tobacco smoker; for women married more than once, only the longest marriage is considered. Exposure to spousal smoking is quantified in units of cigarettes per day or packs of pipe tobacco per week; parental smoke exposure is defined as 0, 1, 2, etc. (equal to the number of parents who smoke). No other sources of ETS exposure are considered. Never-smoking status was checked by comparing the responses to the 1961-63 questionnaires with those obtained in 1984. Data on sources of ETS were not checked. Never-married women were classified as nonexposed to spousal smoke; widows and divorcees were classified according to the smoking status of the former husband with whom they had lived the longest. Of the never-smoking cases for whom passive smoking information was available, squamous and small cell tumors constituted 20 cases, 13 of whom were exposed to spousal smoke; of the other 47 cases, 20 were exposed to spousal smoke.

Responses to the ETS questionnaire were available for a total of 81 never-smoking cases and 347 never-smoking controls. The 67 cases with primary lung or bronchial cancer constitute the ETS study subjects. It is not clear how many of the 347 potential controls were employed in each analysis. Presumably many (up to 4 for each excluded case from the original 81 never-smoking cases) were not used in the matched analysis, whereas most or all were used in the unmatched analyses described subsequently.

A total of 33 of the 67 cases were exposed to spousal smoking. Among the never-smoking women, matched analyses indicate that the odds ratio for marriage to a smoker is 3.8 (95% C.I. = 1.1, 16.9) for squamous or small cell cancer compared with control group 1, 3.4 (0.8, 20.1) compared with control group 2, and 3.3 (1.1, 11.4) compared with both groups combined. For other cell types, corresponding odds ratios are 0.7, 0.8, and 0.8, respectively. Subsequent analyses abandoned matching and pooled all controls. For squamous and small cell cancer, high exposure to spousal smoking (15 or more cig./day or at least one pack of pipe tobacco/week for 30+ years) is associated with an age-adjusted odds ratio of 6.4 (1.1, 34.7), whereas the lower exposure is associated with an odds ratio of 1.8 (0.6, 5.3). The estimated odds ratios for other types of cancer are also elevated for the higher exposure, but not at the lower one. Odds ratios adjusted for age and spousal smoking when at least one parent smokes as well are above 1 (1.9; 95% C.I. = 0.5, 6.2) for squamous and small cell types but not for other types.

it is unclear how important this bias might have been. Lack of consideration of workplace smoke exposure also may have contributed a bias toward the null hypothesis of no association.

The authors addressed a number of potential confounders and risk modifiers. Restriction of subjects to women eliminates potential effects of gender, and age is addressed by retaining age-matching or, alternatively, adjusting for age in all analyses. Reportedly neither occupation, radon, nor urban residence had significant confounding effects, which makes confounding by other factors related to socioeconomic status or lifestyle unlikely, too. An analysis of parental smoking controlled for spousal smoking. The authors do, however, present evidence that the odds ratio for simultaneous exposure to radon and spousal smoke approximately equals the sum of the separate odds ratios for radon and spousal smoke, consistent with additivity of the effects. But, perhaps due to limited numbers, they report results only for all cancers combined rather than for the squamous and small cell subgroup in which the only *significant* spousal smoking association was observed.

In summary, this study reports a consistent, dose-related, and (for high exposure levels) statistically significant positive association between exposure to spousal tobacco smoke and squamous and small cell carcinoma of the lung; a positive but nonsignificant association was also observed for parental smoke exposure. No significant associations were observed for other cell types. The observed associations apparently are not due to confounding by other major risk factors, although dietary and smoking habits were not directly addressed. A possible recall bias cannot be ruled out but seems unlikely given the negative results obtained for cancers other than squamous and small cell. The study provides a useful contribution to investigation of the relationship between ETS exposure and lung cancer.

A.4.26. SHIM (Tier 2)

A.4.26.1. *Author's Abstract*

"A case-control study of Japanese women in Nagoya was conducted to investigate the significance of passive smoking and other factors in relation to the etiology of female lung cancer. A total of 90 nonsmoking patients with primary lung cancer and their age- and hospital-matched female controls were asked to fill in a questionnaire in the hospital. Elevated RR of lung cancer was observed for passive smoking from mother (RR = 4.0; $p < 0.05$) and from husband's father (RR = 3.2; $p < 0.05$). No association was observed between the risk of lung cancer and smoking of husband or passive smoke exposure at work. Occupational exposure to iron or other metals also showed high risk (RR = 4.8; $p < 0.05$). No appreciable differences in food intakes were observed between cases and controls."

A.4.26.2. *Study Description*

This study was undertaken in Nagoya, Japan, during 1982-85 to investigate the significance of passive smoking and other factors such as occupational history, domestic heating system, and dietary habits in the etiology of lung cancer in nonsmoking Japanese women. All data were collected specifically for this study, which was limited to never-smokers.

All subjects were obtained from four hospitals in Nagoya. Cases are women with primary lung cancer (of any type) treated in these hospitals between August 1982 and July 1985 who reported themselves to be never-smokers and consented to interview. Controls are women with a diagnosis other than lung cancer from the same or adjacent wards with controls matched 2:1 with cases on age (± 1 year), hospital, and date of admission. Cases were not restricted to incident disease, but controls were essentially density-sampled by admission date. Data collection was by self-administered questionnaire; no attempt at blinding is described. Of 118 female lung cancer cases treated during the study period, 4 refused to participate in the study and 24 were excluded as current or former smokers. Only a single matching control could be found for 17 of the cases. No other information on loss of potential controls is provided. There is a total of 90 (163) cases (controls), with 52 (91) currently married to a smoker. Cases and controls share identical age ranges (35-81 years) and have nearly identical mean ages (59 years for cases, 58 for controls). All cases were histologically diagnosed, excluding secondary lung cancers.

All study subjects are self-reported never-smokers. A number of individual sources of ETS in the home are considered, including smoking by mother, father, husband, father-in-law, mother-in-law, offspring, and siblings. For each of these sources, smoking in the home at any time constituted exposure. Workplace exposure was characterized simply as presence or absence; for other exposures, the number of cigarettes per day was obtained. In addition, data on length of marriage, time spent in the same room as the wife, and total number of cigarettes smoked were obtained for husbands. Exposure data were not checked, and marital status was not considered in the design or analysis of the study. The predominant type of lung cancer is adenocarcinoma (69 of 90 cases), followed by squamous (13), large cell (4), small cell (3), and adenoid cystic carcinoma (1). No data on airway proximity are provided.

Logistic regression was used to estimate the relative risk for each source of ETS exposure. No significant association with lung cancer was noted for smoking by the husband (RR = 1.1), father (RR = 1.1), husband's mother (RR = 0.8), offspring (RR = 0.8), or siblings (RR = 0.8); smoking by the subject's mother (RR = 4.0) and by the husband's father (RR = 3.2), however, are significant ($p < 0.05$). None of eight dietary factors, including green-yellow vegetable and fruit intake, demonstrated a significant association, nor did type of cooking fuel or frequency of

cooking oil use. Occupational history of exposure to iron or other metals shows a moderately strong but nonsignificant association (RR = 2.8), whereas for use of kerosene, coal, or charcoal heating there is a mild association (RR = 1.6-1.7).

Simultaneous stratification by father-in-law's and mother's smoking indicates that the effects of the two exposures are not additive. Smoking by father-in-law, smoking by mother, and occupational metal exposure were included simultaneously in a logistic regression model. After adjusting the effect of each variable for the other two, the relative risk for maternal smoking, father-in-law's smoking, and metal exposure are 2.1, 3.2 ($p < 0.05$), and 2.4, respectively. The authors conclude that the exposure to tobacco smoke from household members (i.e., mother or husband's father) could be associated with female lung cancer. Because the precise situation of passive smoking in the home or other places is still unclear, however, the authors find that further studies are needed to clarify the significance of passive smoking in relation to the etiology of lung cancer in Japanese women.

A.4.26.3. *Comments*

This study employs a moderate number of well-matched cases and controls. Their comparability appears good, as supported by the identical age ranges and similar mean age and occupational categories for the two groups. A further strength of the study is its lack of reliance on proxy information with attendant potential for inaccurate recall. Exposure information was obtained from self-administered questionnaires, which eliminates the possibility of interviewer bias but may lead to inaccuracy due to misinterpretation of questions or varying care in their completion. Such problems with exposure information would tend to mask any actual association. Lung cancer was histologically diagnosed in all subjects and secondary lung cancers excluded, so diagnostic accuracy appears good for cases. Control diagnoses, however, were not validated, so some smoking-related disorders (in addition to the heart conditions noted in 3% of controls) may be included among the controls, a problem that once again would tend to reduce any observed association.

Restriction of subjects to never-smokers maximizes efficiency because effects of passive smoking would likely be dwarfed by active smoking. But it is unclear precisely what subjects were asked about their smoking status. Were any cut-points regarding past history, duration, or intensity specified? Thus, some misclassification of smoking status may have occurred, and if a greater proportion of persons with smoking family members misreport themselves to be never-smokers, this would create an upward bias.

The authors restrict their assessment of exposure from relatives to at-home smoking, which should be more meaningful than total smoking as a potential source of passive smoke exposure. Furthermore, they collected data on smoking habits of all relatives, not just spouses or parents, thus reducing the chance of missing an exposure source. On the other hand, there is no consideration of total household smoking (all sources combined), cumulative exposure (except for husbands), or of pipe or cigar smoking; nor is there differentiation of current and former exposure--all potential sources of exposure misclassification, which would tend to make an association more difficult to detect.

Of the several sources of ETS exposure at home, only the relative risks for smoking by the mother and by the father-in-law are suggestive, and both of these are significant ($p < 0.05$). When these sources are considered simultaneously, however, and the effect of each is adjusted for the other, smoking by the husband's father remains significant (RR = 3.2; $p < 0.05$) but the effect of mother's smoking is diminished (RR = 2.1) and is not statistically significant. Exposure from the father-in-law is, of course, in adulthood. There is no evidence of an effect from husband's smoking (RR = 1.1), however, and these exposure sources were considered simultaneously so that the effect of one could be adjusted for the other. The large number of comparisons (e.g., eight groupings of passive smoke exposure, alternative spousal exposure measures, several occupational factors, and eight dietary factors) increases the likelihood that an observed relative risk will appear to be significant by chance alone (the effect of multiple comparisons).

Another aspect of the statistical analysis worth noting is that, although cases and controls appear well matched on age, hospital, and hospital admission date, these factors are not included in an adjusted analysis of the data (aside from the example with three sources of exposure described above). Consequently, some bias due to these factors is a possibility, although the demographic similarities between cases and controls makes a large effect unlikely.

In summary, this study presents some interesting results. It finds a strong (adjusted RR = 3.2) and statistically significant association between father-in-law's smoking at home and lung cancer and associations for maternal smoking and occupational metal exposure as well. The lack of association for any of the other sources of ETS examined could be due to problems with exposure assessment and control disease criteria. Equally, however, given the unclear treatment of matching factors in the analysis and the number of variables explored, the few substantial associations noted might be due to chance, confounding, or both. Were potential confounders clearly treated in their analyses, this study would have made a stronger contribution. As it stands, the study's data are of moderate utility, providing the number of comparisons and limitations regarding bias are kept in mind.

A.4.27.3. ***Comments***

With 144 cases and 731 controls, the sample size is larger than many of the other case-control studies on ETS. Information on cases and controls was obtained by self-administered questionnaire, which is generally considered less reliable than face-to-face interviews. The questionnaires were presumably completed by the subjects themselves in all cases, however, which is preferable to proxy-supplied information. The information supplied was not verified from other sources, as noted by the authors in reference to testing for biomarkers of exposure to tobacco smoke (they note that laboratory tests can only detect recent exposure, but they could still be useful in eliminating current smokers who may misreport themselves as never-smokers). Although cases and controls were newly diagnosed patients within a short time period in the eight participating hospitals and were supplied with the same questionnaire, there are still some questions regarding the comparability of cases and controls and their representativeness of the target population.

Controls tend to be younger than cases: While mean ages are 56 and 60, respectively, 33% of controls, compared with 14% of cases, are below the age of 40. Controls also tend to be more educated than cases, with 69% of controls having completed 10 or more years of education compared to 52% of cases. Differences in age and educational level further reflect differences in lifestyle and socioeconomic status that may affect risk of disease. Also, the controls are predominantly cancer patients too, almost half with breast cancer, suggesting that the controls may be a biased sample (as noted by the authors). On the other hand, exclusion of breast cancer controls reportedly leaves the results unchanged. Furthermore, the statistical analysis stratifies on age and education, so even though cases and controls were not strictly matched on these variables, the reported results should not be due to confounding by either of these factors.

Although some of the issues and reservations described above are methodological in nature and apply to the study throughout, others are specific to the ETS data alone. For example, one might expect a question regarding the use of cooking with wood or straw at age 15 and at age 30 to be open to little subjective interpretation or error in recall, presuming that methods of cooking persisted for several years between changes within a household. Although there is some suggestive evidence of increased lung cancer from ETS exposure, the statistical evidence may be stronger for an association between lung cancer and use of wood or straw for cooking at age 30. Further support is provided by the observation that among those who had used wood or straw for cooking at age 30, 90% had also used those fuels at age 15, suggesting extended exposure in most cases. The age distribution of those exposed to wood or straw cooking is not given, but exposure at

participating hospitals were experienced specialists in lung cancer. Thus, the likelihood of secondary lung cancers among the cases should be small.

Several sources of ETS exposure are included, all of which occur in the home. Exposure in adulthood is expressed by two measures--smoking by the husband and other household members (the last category consists chiefly of households where the husband's father and/or sons smoke). Three sources of exposure in childhood are considered--father smokes, mother smokes, and other household members smoke. No information is provided on how exposure to spousal smoking is handled for unmarried women (single, divorced, or separated). The entire complement of cases and controls is included in the summary data for each of the five sources of exposure given above. If only married women were included in the study, no mention of it was found.

The histological data for ETS subjects are not classified by exposure to ETS, but the percentage of cases by cell type are given: squamous cell (8), small cell (5), adenocarcinoma (78), large cell (5), and other (4). The ETS data on spousal smoking consists of 80 of 144 (exposed/total) cases and 395 of 731 controls, for an odds ratio of 1.13 (95% C.I. = 0.78, 1.63). (Our calculations give 1.06 [0.74, 1.52].) The odds ratio for ETS exposure from other household members in adulthood is 1.57 (95% C.I. = 1.07, 2.31). (Our calculated values are 1.77 [1.21, 2.58].) For ETS exposure in childhood by the father, mother, and by other household members, the respective odds ratios are 0.79 (95% C.I. = 0.52, 1.21), 1.33 (95% C.I. = 0.74, 2.37), and 1.18 (95% C.I. = 0.76, 1.84). Tests were conducted by the Mantel-Haenszel procedure, with stratification by age and education (two levels). Analysis by logistic regression, adjusted for age at time of hospitalization, was conducted for two of the exposure measures described above with similar outcomes. Based on this evidence, the author concludes that for childhood exposure, a slight increase of risk was suggested for those with smoking mothers, although statistical significance was not observed. For exposure in adulthood, an elevated risk was estimated for those with smoking household members other than husbands.

The statistical analysis includes exposure to sources other than ETS, namely, the use of wood or straw as cooking fuel, the use of heating equipment that pollutes the room with combustion products, and the use of charcoal foot warmers. All exposures considered, including ETS, are smoke or fumes from products burned indoors. It is concluded that significantly elevated risks were observed for subjects who had used wood or straw as cooking fuels at 30 years of age (OR = 1.89; 95% C.I. = 1.16, 3.06). No elevated risks were found for sources of indoor heating (use of kerosene, gas, coal, charcoal, and wood stoves without chimneys). Similarly, no significance was found for the use of charcoal foot warmers, a practice that was popular until the 1960s.

Sweden, and 209 age-matched population controls were interviewed about their exposure experiences according to a structured questionnaire. A strong association between smoking habits and lung cancer risk was found for all histological subgroups. Relative cancer risk was found for all histologic subgroups. Relative risk for those who had smoked daily during at least 1 year ranged between 3.1 for adenocarcinoma to 33.7 for small cell carcinoma in a comparison with never-smokers. All histological types showed strong dose-response relationships for average daily cigarette consumption, duration of smoking, and cumulative smoking. There was no consistent effect of parental smoking on the lung cancer risk in smokers. Only 38 cases had never been regular smokers and the risk estimates for exposure to environmental tobacco smoke were inconclusive. The high relative risks of small cell and squamous cell carcinoma associated with smoking may have relative implications for risk assessments regarding passive smoking."

A.4.29.2. *Study Description*

This study was undertaken in Stockholm County, Sweden, from 1983 to 1986 to investigate the association between female lung cancer and some possible etiologic agents, particularly active and passive smoking. Because active smoking was an exposure of interest, cases and controls were not matched on smoking status; thus, the ETS study population is unmatched.

Cases are Swedish-speaking women with primary lung cancer from three Stockholm County hospitals who were willing and able to be interviewed between September 1983 and December 1985. Cases with carcinoid tumors were excluded from the ETS analysis. Both population and hospital-based control groups were assembled. Population controls were women randomly selected from the county population register, matched to a case on birthdate and interviewed between September 1983 and December 1986. Hospital controls were subjects originally interviewed as potential lung cancer cases but subsequently diagnosed with nonmalignant conditions. Population controls were enlisted and interviewed as soon as a case's diagnosis was confirmed, but because this confirmation took as long as a year after the interview, controls were not density sampled. Unblinded interviews were conducted face-to-face with all cases (and hospital controls) and 58% of the total population controls; the remainder were interviewed by telephone.

After exclusion of 21 potential cases due to initial diagnostic uncertainty, refusal, or illness precluding interview, 210 confirmed cases remained. Elimination of 172 ever-smokers and four subjects with carcinoid or not-microscopically-confirmed tumors left 34 never-smoking cases. Similarly, 209 population and 191 hospital controls were included in the total study, but a combined total of only 174 were never-smokers. The total case population averaged 62.5 years of

age, but no other demographic information regarding cases or controls is provided. All cases used in the ETS analyses were histologically or cytologically confirmed primary lung cancers.

Daily smoking for at least 1 year is the criterion for a smoker; all other persons are considered never-smokers. Pipe and cigar smoking are never specifically addressed. Exposure to ETS is calculated for four sources: mother, father, home, and work. Having a smoking mother or father (at any time during ages 0-9 years) constitutes exposure to that particular source, whereas the presence of a smoker at home and work constitutes exposure. Adulthood and total lifetime exposure are considered separately for home and workplace exposure. Exposure levels are arbitrarily scored 1 for nonexposure, 2 for exposure to one source, and 3 for exposure to both sources in trend analyses of never-smokers, where exposures are considered in pairs (i.e., maternal and paternal smoking, home and workplace exposure). No other units of ETS exposure are used. Adenocarcinomas constituted 22, squamous cell 5, and small cell 2 of the 34 lung cancers occurring among never-smokers in the ETS population; no further histologic details regarding the ETS study population are provided.

To maximize available case numbers, parental smoking was first analyzed among all cases and community controls using stratification to adjust for active smoking (cig./day) and age. A risk of 1.8 (95% C.I. = 0.5, 7.0) was estimated for maternal smoking and 0.8 (0.3, 1.4) for paternal smoking. A trend analysis in which maternal, paternal only, and no parental smoke exposure were scored as 3, 2, and 1, respectively, revealed no indication of trend ($p = 0.9$). Analyses restricted to never-smokers used both community and hospital-based controls combined. Among cases (controls), for childhood up through 9 years of age, 3 (5) had smoking mothers, 12 (71) had smoking fathers (but not mothers), and 19 (98) were unexposed. This yielded an age-adjusted risk estimate of 3.3 for maternal smoking (with or without paternal smoking) and 0.9 for paternal smoking during childhood. Adult exposure at home *and* at work yielded an estimated risk of 2.1, whereas exposure at home *or* work yielded a risk of 1.2. For lifetime exposure, the estimated risks for exposure as both a child *and* adult and as either a child *or* an adult were 1.9 and 1.4, respectively. None of these associations were statistically significant, and no significant trends were observed. The authors conclude that the results pertaining to ETS in the present study were not conclusive. The small number of never-smokers among the cases could be one important reason. It should be noted, however, that most of the point estimates of relative risk were greater than unity, which agree with results from previous studies on ETS exposure and with risk estimates concerning active smoking.

A.4.29.3. *Comments*

This study was undertaken to explore the role of active as well as passive smoking in lung cancer. After exclusion of active smokers, the available number of cases is too small to yield much statistical power.

Cases and population-based controls were initially matched on date of birth, but this matching was abandoned in the ETS analysis; furthermore, unmatched hospital-based controls are combined with the population-based controls in most analyses to boost available numbers. The comparability of these groups is thus unclear, and the authors provide no demographic comparisons to facilitate assessment of this potential problem. The reported similarity of results using only population-based controls is reassuring, but no details are provided as to *how* similar results actually were.

Diagnostic misclassification of cases is unlikely, given the histological or cytological confirmation of all cases and exclusion of secondary cancers. All cases were interviewed face-to-face, but 42% of controls were interviewed by telephone. The accuracy of responses may thus be lower for controls than for cases. In addition, because interviews were not conducted blindly, inflation of estimated associations through interview bias is possible. A potential bias is also introduced by the rather large amount of active smoking required for classification as an ever-smoker. This allows considerable active smoking among persons in the never-smoker group, the effect of which could mask an effect of passive exposure, or, if co-varying positively with passive smoking, cause overestimation of association.

The first set of analyses of paternal and maternal smoking includes ever-smokers while attempting to adjust for active smoking on the basis of average daily cigarette consumption. The adequacy of this adjustment is questionable given the large estimated risks associated with active smoking relative to those posited for passive smoking, so the elevated estimated risks for maternal smoking obtained in these analyses are of questionable validity.

Restriction of the analyses to never-smokers similarly produces an elevated odds ratio for maternal smoking of 3.3, but the numbers involved (three cases and five controls) are so small that this value is quite unstable. A pattern of increasing estimated risk with increasing sources of exposure (at home or at work) as an adult and increasing periods of exposure (in childhood or adulthood) over the lifetime is suggestive of an association between lung cancer and ETS, but again small numbers preclude statistical significance of these results.

Restriction of the study population to females rules out the possibility of a gender-related effect. The likelihood of an ethnicity effect is reduced by restriction to Swedish-speaking residents of Stockholm County, and age is reportedly controlled for in all analyses. No other

potential risk modifiers are addressed. For example, marital status is not considered in the analyses of spousal smoking, leaving open the possibility that nonsmoking-related differences between married and unmarried women contributed to the observed association. The reported similarity of results when only population controls were used instead of hospital and population controls combined provides a general argument against bias due to source of controls, although no specifics regarding the degree of similarity were supplied.

In summary, this study presents consistent evidence of associations between lung cancer and maternal, home, and workplace passive smoking exposure. Limited numbers preclude statistical significance, and interviewer bias or effects due to dietary or other factors cannot be ruled out as contributors to the observed results. Bearing these limitations in mind, the study's results are inconclusive but (excluding the analyses that include active smokers) do make a useful contribution to the pool of information available regarding ETS and lung cancer.

A.4.30. TRIC (Tier 3)

A.4.30.1. *Author's Abstract*

"Fifty-one women with lung cancer and 163 other hospital patients were interviewed regarding the smoking habits of themselves and their husbands. Forty of the lung cancer cases and 149 of the other patients were nonsmokers. Among the nonsmoking women, there was a statistically significant difference between the cancer cases and the other patients with respect to their husbands' smoking habits. Estimates of the relative risk of lung cancer associated with having a husband who smokes were 2.4 for a smoker of less than one pack and 3.4 for women whose husbands smoked more than one pack of cigarettes per day. The limitations of the data are examined; it is evident that further investigation of this issue is warranted."

A.4.30.2. *Study Description*

This study was undertaken in Athens, Greece, to investigate the relationship of spousal smoking and lung cancer. All female Caucasian Athenian residents admitted to one of three chest or cancer hospitals in Athens and assigned a final diagnosis of lung cancer other than adenocarcinoma and alveolar carcinoma from September 1978 through June 1980 were interviewed by a physician. Controls were gathered from nonsmoking female Caucasian Athenian patients hospitalized during the same time period in the Athens Orthopedic Hospital. Some prevalent cases were thus presumably included, so control sampling probably approximated a density approach but did not strictly conform to one.

representative of the general community than of hospitalized patients as a whole. This should reduce the problem of inclusion of smoking-related illnesses in the control group.

Although the researchers sought to exclude adenocarcinomas and alveolar carcinomas, presumably considering these would be less smoking related, nearly two-thirds of the cases were not histologically confirmed, so an indeterminate number of these cell types was probably included. More important, the infrequency of histologic confirmation and lack of mechanisms to verify diagnoses or primary tumor status introduces potential for misclassification. The likely effect is a bias toward no association.

The researchers clearly devoted considerable thought to the smoking and exposure criteria, particularly with regard to changes in smoking and marital status over time. Single women were, however, automatically classified as unexposed. The authors contend that this is warranted by the traditional nature of Greek society and report that analyses restricted to married women result in similar, and still statistically significant, associations, although with somewhat lower estimated risks. There is a small reduction in the odds ratios after exclusion of single women, however, and the restriction of the full analyses and results to married women may have been useful.

Another issue related to exposure concerns inclusion of former smokers in the study, provided they had not smoked for at least 20 years. Active smoking 20 to 30 years before the onset of lung cancer may be of etiological relevance, however, in view of a long latency period for lung cancer. Although use of the same interviewing physician for all subjects eliminates the problem of interobserver variability, it leaves open the potential problem of interviewer bias in exposure assessment, presumably toward a positive association, because the interviews were apparently conducted unblinded (virtually unavoidable with regard to diagnosis, given that controls were drawn from orthopedic trauma and rheumatology wards).

A larger concern, however, is the potential effect of risk factors or modifiers not addressed in the analysis. The authors contend that the similar distribution of demographic variables between cases and controls eliminates the need to consider these variables in the analyses, but adjusting for relevant variables is recommended even in a matched study (see Section 5.4.1). More convincing is the contention that these variables were not significantly associated with smoking in these data, although no specifics are included. The appearance of a statistically significant trend for ETS exposure measured by either current spousal smoking or cumulative cigarette consumption during marriage lends further support to an association between spousal smoking and increased lung cancer incidence. Potential factors such as diet, cooking, and heating practices, however, are not addressed.

Overall, the issues addressed above would probably produce a conservative bias, resulting in an underestimate of the degree of association. The study's basic design is sound. It provides

The authors note that this study has obvious limitations and is offered principally to suggest that further investigation of this issue should be pressed. Most seriously, the numbers of cases are small. Nevertheless, the association is in the direction expected if passive smoking is related to lung cancer, and the outcome is unlikely to be due to chance. Other limitations noted include the high percentage (35%) of cases lacking cytology and the selection of controls from a hospital different from those of the cases; it is argued, however, that neither of these appears to be consequential. The observation is made that it is potentially easier to detect an effect of passive smoking in the Greek population than in most Western populations, because in the latter groups, the overwhelming effects of active smoking, together with the high correlation between smoking habits of spouses, would tend to confound and conceal the lesser effects of passive smoking.

A.4.30.3. *Addendum*

In a letter to the editor of *Lancet* in 1983, Trichopoulos et al. released a data table derived from extension of subject collection through December 1982. This nearly doubled the sample size used in the 1981 publication, yielding 77 nonsmoking cases (102 total) and 225 smoking controls (251 total). The crude odds ratio calculated by the reviewers is 2.08 (95% C.I. = 1.20, 3.59). The results for the expanded study show very little change; (estimated) relative risks when husbands are former smokers (1-20 cig./day and > 20 cig./day) compared with nonsmokers are 1.95, 1.95, and 2.54, respectively. The test for upward trend in the dose-response is significant ($p = 0.01$). No other analyses are presented.

A.4.30.4. *Comments*

This study was conceived and undertaken to explore the association of spousal smoking with lung cancer and does not rely on a preexisting data set. Thus, the investigators were in a position to design their selection and data collection to maximize the strength of their findings. This did not, however, prevent the appearance of some design and analytical flaws.

Demographics of the total case and control populations are very similar. All subjects in the spousal smoking analysis are resident Athenian nonsmoking women hospitalized in the same area of Athens; case and control groups have very similar mean ages, and their husbands are comparable in education. Thus, the groups probably have good demographic comparability, although it would have been helpful if the detailed demographic comparisons were focused on the nonsmokers alone. Most of the controls (108 out of 163) were being treated for fractures, a relatively minor and nonchronic illness compared with lung cancer, which may make them more

interviewed due to illness, refusal, or other reasons did not differ significantly in demographic or smoking status from those actually interviewed, again arguing against biased selection.

No proxy interviews were used, and all subjects were English-speakers, enhancing the chances of obtaining accurate exposure information. On the other hand, interviews were by telephone--possibly decreasing accuracy relative to face-to-face interviewing--and apparently unblinded, thus introducing possible interviewer bias toward positive results.

Collection of exposure data seems generally adequate, except that treatment of pipe and cigar smokers is not described. This is coupled with an uncertain definition of parental smoking and lack of treatment of household smokers other than parents or spouses in the analyses, despite collection of data on this point. These uncertainties probably translate into nondifferential exposure misclassification, biasing results toward the null.

The analyses suffer from the common problem of restricted numbers of nonsmoking cases--29 for adenocarcinoma and only 2 for squamous cell. Some factors examined are restricted to nonsmokers alone for adenocarcinoma, but for most analyses, an adjustment for active smoking by logistic regression modeling was attempted. The adequacy of such adjustment may be questionable. For adenocarcinoma, however, the results for passive smoking were very similar, regardless of whether restriction or adjustment was used. Further, a dose-response pattern was seen for cumulative years of spousal and workplace exposure among nonsmokers. The results of the analyses for squamous cell are too unstable to be meaningful, given the paucity of cases.

The findings of substantial associations between lung cancer (or, at least, adenocarcinoma) and childhood pneumonia and coal burning are of interest. It must be borne in mind that seven adult respiratory diseases (including pneumonia) as well as six other childhood respiratory diseases were examined, so the possibility that the pneumonia association was an artifact of multiple comparisons cannot be ruled out. History of hysterectomy and multiparity showed nearly significant associations with adenocarcinoma, but it is not clear how many other health history factors also were considered. Coal burning has been associated with lung cancer in several other studies. Similarly, as in several other studies, one found an association with low beta carotene intake, but there was no evidence of a dose-response gradient, and no significant association was found for preformed vitamin A. The strongest association with a dietary factor was actually that for low intake of dairy products and eggs, which showed a consistent dose-response pattern. The use of a matched-pair analytical approach controls for effects of age or neighborhood, which also reduces the likelihood of neighborhood-related factors such as socioeconomic status as major sources of bias. Confounding due to active smoking can be ruled out in the passive smoking results for adenocarcinoma and is not likely in regard to other factors given adjustment for this variable in all analyses. Likewise, the authors report that adjustment for childhood pneumonia,

For squamous cell cancer, maternal, paternal, spousal, and workplace relative risks are 0.2, 0.9, 1.0, and 2.3, respectively. None of these estimates is statistically significant.

History of lung disease at least 5 years prior to diagnosis of lung cancer reportedly had no significant association with lung cancer. History of lung diseases before age 16 yielded a significant association for pneumonia (RR = 2.7 [95% C.I. = 1.1, 6.7] for adenocarcinoma and RR = 2.9 [95% C.I. = 0.5, 17.4] for squamous cell cancer) but not for six other diseases.

Heating or cooking with coal during the childhood and teenage years is also significantly associated with lung cancer (RR = 2.3 [95% C.I. = 1.0, 5.5] for adenocarcinoma and RR = 1.9 [95% C.I. = 0.5, 6.5] for squamous cell). Among dietary factors, low beta carotene consumption is significantly associated with adenocarcinoma (RR = 2.7) and mildly associated with squamous cell (RR = 1.5). Diets low in dairy products and eggs have similar relative risk values. No significant associations were noted for vitamin A consumption, occupation, or other health history factors not previously considered.

The authors conclude that the etiology of squamous cell carcinoma can be explained almost entirely by cigarette smoking. Cigarette smoking, however, explains only about half of the adenocarcinoma cases. On the basis of this study, childhood lung disease and exposure to coal fires in childhood explain at least another 22% of adenocarcinoma cases. Passive smoking and vitamin A may be involved, but more research is needed to clarify their roles in lung cancer etiology.

A.4.31.3. *Comments*

This study took particular care with its treatment of case and control assembly. Extensive inclusion criteria extending to both groups, matching not only on age but neighborhood of residence, and retention of matching through analysis all bode well for comparability of cases and controls. The virtually identical mean ages of cases and controls indicate the success of these efforts. In addition, exclusive use of incident cases reduces the potential for selection bias, and density sampling of controls reduces potential problems with temporal variation. The only real fault in the treatment of cases and controls is the failure to provide any demographic comparison other than for age, thus denying concrete confirmation of the expected high case-control comparability.

Case diagnoses are likely to be accurate, because all were histologically diagnosed, making misclassification unlikely and making cell-type-specific analyses possible. Although no one pathologist or team verified these determinations, the authors note that there is generally good interobserver agreement for the cell types included in this study. Potentially eligible cases not

A.4.32.2. ***Study Description***

The objective of this study was to evaluate the role of potential risk factors for lung cancer in Harbin and Shenyang, two cities among those with the highest mortality rate for lung cancer in China. Active smokers are included in the cases, so data on ETS subjects constitute a subset of the whole study.

Cases consist of female residents under age 70 newly diagnosed with primary lung cancer in about 70 participating hospitals in Harbin and Shenyang between 1985 and 1987. Controls are female residents randomly selected from the general population of these cities and frequency matched by 5-year age group to the age distribution of female lung cancer cases reported in the cities in 1983. Trained interviewers collected information on smoking habits, diet, cooking and heating practices, and other factors from subjects in face-to-face unblinded interviews.

A total of 1,049 qualifying cases were found, including both ever-smokers and never-smokers, of which 405 were diagnosed by histology, 309 by cytology, and 351 by radiology or clinical means. (*Note*: These diagnostic numbers do not total 1,049. The 351 figure may be intended to be 251, which would give a total of 965 diagnoses, about the number of cases interviewed.) Of these, 85 either died prior to interview, refused to participate, or could not be located. Mean age of participating cases was 55.9 years, whereas that of the 959 controls was 55.4 years. Nonsmokers compose 417 of the interviewed cases and 602 of the controls.

A smoker is defined as a person who has smoked cigarettes for 6 months or longer, so a nonsmoker apparently may have smoked for up to 6 months. Information on all types of tobacco products smoked was collected. Sources of ETS exposure include smoking by any household cohabitant and smoking by individuals (spouse, mother, and father) over the course of the subject's lifetime. Exposure at the workplace is also addressed. ETS exposure in the home is expressed in terms of cigarettes per day and number of years smoked; no units of measurement are used for workplace smoking. No checks on exposure data were undertaken. Marital status of subjects is not discussed. Of the cases with histological or cytological data, adenocarcinomas compose 310 (41.7%), squamous cell cancers 201 (28.9%), small and oat cell cancers 117 (16.8%), and large cell or unspecified types 66 (9.5%). No data on airway proximity or diagnostic breakdowns limited to nonsmokers are provided.

Statistical analyses of potential risk factors, including ETS, largely include data on active smokers and then adjust for the effect due to smoking by logistic regression, along with other potential confounders such as age, education, and location (Shenyang vs. Harbin). These analyses indicate no increase in risk from household sources of ETS, with estimated relative risks of 0.8 (household cohabitants), 0.9 (spouse), 1.0 (mother), and 1.0 (father). The estimated risk for

workplace exposure is nonsignificant (RR = 1.2). Restriction of analyses to ETS subjects alone (i.e., only the nonsmokers) produced similar results, with estimated relative risks of 0.7 for general cohabitant, 0.7 for spouse, 0.9 for mother, 1.1 for father, and 1.1 for workplace exposure. The ETS exposure from spousal smoking is significantly low (i.e., associated with a decrease in lung cancer by this analysis, as apparent from the confidence interval; RR = 0.7; 95% C.I. = 0.6, 0.9).

The smoking-adjusted analyses indicate associations with lung cancer for several types of heating devices, including kangs (brick beds heated by pipes from the stove or by burners directly underneath), coal stoves, and heated brick walls or floors. The risk associated with the use of burning kangs (those heated by stoves underneath) shows an upward trend with years of use, becoming statistically significant at 21 or more years of use (RR = 1.5; 95% C.I. = 1.1, 2.0). Significantly elevated risks are also associated with use of heated brick walls or floors (RR = 1.5 [1.1, 2.1] for 1-20 years of use; RR = 1.4 [1.1, 1.9] for > 20 years). Nonsignificant increases in risk are noted for use of kangs of all types, coal stoves, and coal burners; nonsignificant reductions in risk are indicated for noncoal stoves and central heat. Deep-frying cooking at least twice a month and eye irritation during cooking are both significantly associated with lung cancer, as are regular intake of animal protein and fresh fruit. (*Note*: Multiple comparisons may be a factor for the apparent significance of some items, as discussed further in the next section.)

The authors find no overall association between lung cancer and ETS exposure. On the other hand, coal burning, exposure to cooking oil fumes, and chronic lung disease all may be risk factors. Consumption of beta carotene shows no evidence of a protective effect. Overall, active smoking is the major cause of lung cancer among women in the regions sampled.

A.4.32.3. *Comments*

The sample size is impressive, with ETS exposure data available for nearly 1,000 cases including smokers and more than 400 cases when restricted to nonsmokers, thus providing substantial statistical power. All subjects are women recruited from two industrial cities in northeast China, reducing potential for complications due to regional or urban-rural differences. Nearly all of the hospitals in these cities were involved, all cases occurring in these hospitals were targeted, and the rate of participation among eligible cases was high; thus potential for selection bias is minimized. The effective case recruitment in combination with the use of general population controls maximizes generalizability of the study's results for northeast China. It would have been useful, however, to present the results for the two component study locations separately. Although coordinated in planning and execution, there are two separate study